REVIEW ARTICLE

THE NEW-GENERATION ANTIPSYCHOTICS —INTEGRATING THE NEUROPATHOLOGY AND PHARMACOLOGY OF SCHIZOPHRENIA

Brian H Harvey, Dan J Stein, Robin A Emsley

Despite a well-established role for dopamine (DA) in the neuropathology of schizophrenia, and the evidence of a hyperdopaminergic state in the schizophrenic brain, many questions still remain. Typical agents acting predominantly on DA D_2 receptors are only partially effective. New data now indicate that the interaction between DA and the various DA receptors as well as DA interaction with other transmitter systems, are more critical in deciding the therapeutic success of an antipsychotic than actions on DA alone. These interactions are closely associated with what is being documented regarding the neuro-anatomy, neurobiology and neuropsychology of the disorder.

There have been major advances in the understanding of the neuropathology of schizophrenia that, while not replacing the original DA hypothesis, have forced a re-evaluation of our understanding of the disorder. In this paper we present the biochemical and neuropathological basis for schizophrenia and discuss six new atypical antipsychotics according to these theories. Drugs reviewed include clozapine, risperidone, olanzapine, ziprasidone, sertindole and quetiapine.

While not a comparative analysis of these drugs, this paper is an appraisal of how their pharmacology correlates with our present knowledge of the disorder and highlights differences among the drugs in this group. These agents therefore possess specifically designed qualities, to varying degrees, promising a significant improvement over earlier agents in terms of treating positive and negative symptoms, with a minimal risk of extrapyramidal symptoms (EPS). These qualities include an emphasis on D_2 selectivity, D_1/D_2 balance, DA/serotonin (5HT) balance, D_3/D_4 selectivity, DA/acetylcholine (Ach) balance and glutamate (Glu)/gamma-aminobutyric acid (GABA) balance. The drugs are discussed with reference to these criteria.

Targeted drug design has created a goal-directed strategy with which to treat schizophrenia. These new antipsychotics appear to have several distinct advantages over their predecessors, and should make a major contribution to the treatment of schizophrenia and the re-integration of these patients into society.

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Schizophrenia is an extremely debilitating disorder that often presents with a poor long-term prognosis. Despite the proven efficacy of the neuroleptic agents currently available, outcome statistics still reflect a disorder that is difficult to treat. These statistical data emphasise the hidden costs associated with schizophrenia, and suggest an urgent need for new and more effective treatment strategies. Approximately 50% of discharged patients will be rehospitalised within a year. Two-thirds of first-episode patients continue to experience positive symptoms after a year, and about one-third will continue to have them after 6 years.[1] Less than 20% of schizophrenics are employed at any one time.[1] Patient scores on subjective and objective measures of quality of life are very poor, and 10% of patients with schizophrenia will commit suicide.[1] On the issue of drug treatment, 20% of schizophrenic patients experience a relapse despite antipsychotic medication,[2] while approximately two-thirds of patients on medication for schizophrenia experience persistent parkinsonism.

There is now strong evidence to support the suggestion that the long-term outcome of first-episode schizophrenia can be significantly influenced by the choice and dose of agent made at the start of treatment.[3] Pharmacotherapy is often more successful in these patients, while studies also reveal that they respond better at lower doses. They are also more sensitive to extrapyramidal symptoms (EPS). Recent data also suggest that there is no advantage in using higher than nominal doses in treatment-resistant cases[4] and that the equivalent of 100 - 700 mg/day of chlorpromazine constitutes an adequate dose range for most psychotic patients.[2] Consequently, since experiencing a dystonic reaction may influence long-term compliance and possibly be a risk factor for relapse,[3] use of an agent with low EPS liability, or using a lower dose, will have significant impact on the overall outcome. In addition, after each subsequent relapse there is a drop off in response to treatment,[3] resulting in the long-term morbidity figures quoted earlier. Therefore, a good response from the outset predicts a better outcome, and all these points can be significantly influenced by the choice of

School of Pharmacy, University of Potchefstroom, North West
Brian H Harvey, BPharm, BSc Hons (Pharmacol), MSc, PhD
Department of Psychiatry, University of Stellenbosch, Tygerberg, W Cape
Dan J Stein, BSc (Med), MB ChB, FRCPC
Robin A Emsley, MB ChB, MMed (Psych), MD

medication. Experience with clozapine indicates that such a prudent choice can reduce hospitalisation and indirect costs associated with the illness.[1] Despite their initial high cost, therefore, the use of a new improved agent as first-line choice may have significant cost-effective benefits in the long-term management of schizophrenia.

Although the exact cause of schizophrenia is still unknown, innovative and pioneering research into the pathogenesis of schizophrenia is revealing new information about this enigmatic disorder. As research probes this frontier, the ensuing observations and ideas are becoming instrumental in providing pharmaceutical chemists with neurobiological targets around which potentially new and better agents are being developed. The initial observations demonstrating the antipsychotic action of D_2 receptor antagonists, such as chlorpromazine and haloperidol, were instrumental in shaping our understanding of schizophrenia. Later, greater emphasis on dopamine (DA) D_2 receptor selectivity led to the proposed value of the D_2-specific actions of sulpiride and other substituted benzamides. In more recent years, the realisation of the critical role of serotonin (5HT) and its potential role in the modulation of EPS induced by overt D_2 blockade has led to the development of $D_2/5HT_2$ receptor antagonists, including ziprasidone, sertindole and risperidone. Finally, the well-established clinical efficacy and favourable EPS profile of clozapine, fuelled by observations that schizophrenia is probably an imbalance in DA as well as disturbed 5HT, glutamate (Glu), acetylcholine (Ach), gamma-aminobutyric acid (GABA) and neuropeptide function, has rekindled interest in the role of the multireceptor antagonist. This has paved the way for the development of clozapine-like agents such as olanzapine and quetiapine.

While antipsychotics have in the past been classified in various ways, e.g. chemical structure, therapeutic effects, receptor affinities and as atypical/typical, it would appear more logical to classify the new atypical agent according to the specific concept of the neuropathology of schizophrenia that has spawned its development. All the agents discussed in this paper, but especially risperidone, ziprasidone and sertindole, exploit the benefits of a high $5HT_2/D_2$ receptor-blocking ratio, proposed to be crucial in both an improved efficacy with regard to negative symptoms and inducing a low incidence of EPS. Olanzapine, quetiapine and clozapine, while also displaying prominent $5HT_2$ over D_2 antagonism, also act at various other receptor sites, which the aforementioned three have less affinity for, and which may have additional benefits for the overall treatment of the disorder. These include antimuscarinic actions, alpha-2 adrenoceptor antagonism, Glu actions, D_1 antagonism and D_3/D_4 antagonism. However, affinities for alpha-1 and histamine H_1 receptors carry a side-effect risk that may vary from one agent to the next. No doubt as we learn more of the neurobiology of the illness, new approaches to treating schizophrenia will become available.

There are various candidate atypical agents in development. Some, like zotepine, follow the same rationale as those discussed in this paper.[2] However, there are a few agents that are attempting to tread new ground. Two promising options are the concept of the partial dopamine agonist, while another is to focus on the glutamate hypothesis of schizophrenia. The ideal partial agonist with suitable intrinsic activity should be as efficient as the dopamine antagonists in attenuating psychotic symptoms by preventing absolute or relative hyperdopaminergia, but should be unable to induce hypodopaminergia that would result in troublesome motor and mental side-effects.[5] L-701,324 is a full antagonist at N-methyl-D-aspartate (NMDA) receptor sites and pre-clinical data suggest an atypical neuroleptic profile,[6] while D-cycloserine, a partial NMDA-glycine site agonist, has similarly shown promise as an atypical agent.[7]

Despite there being much debate on the definition of the 'atypical' antipsychotic and what properties confer 'atypicality', this classification has nevertheless found favour due to its conceptual appeal and seductive simplicity. However, these very same attributes may be inappropriate and misleading for various reasons.

Firstly, there is no generally accepted definition of the concept 'atypical'. The most widely used criterion is a low level of EPS, but it is not unusual to include other criteria such as a low level of tardive dyskinesia (TD), no prolactin release and a beneficial effect on negative symptoms in patients who are poor responders. Whether a particular agent exerts primarily a direct anti-negative action or is secondary to its lower motor side-effects, antidepressant action and/or antipsychotic action, remains an issue that is often difficult to interpret from clinical trials. This has been overcome to some extent with the use of a path analysis, although further work is still required.[8] This analysis determines whether a significant difference still remains after co-varying the negative symptom response with the above three effects of the drug. Secondly, the atypical antipsychotic group encompasses compounds that display a wide variety of pharmacological effects, ranging from pure D_2 antagonists to multiple receptor antagonists. Finally, the atypicality of an agent has entailed a strong focus on EPS to the detriment of other side-effects, such as weight gain and sexual disturbances. The new atypicals are characterised by these side-effects to varying degrees.

This paper will attempt to determine the extent to which the newer agents have improved the pharmacotherapy and outcome of schizophrenia by examining their individual pharmacological properties. The ultimate comparison will be through controlled clinical trials. However by examining the pharmacology of these agents and using a new paradigm created by the latest thinking around the aetiology and neuropathology of schizophrenia, some speculative ideas can be put forward.

NEUROCHEMISTRY OF SCHIZOPHRENIA — RELATION TO THE NEW-GENERATION ANTIPSYCHOTICS

Role of DA and its relevance to schizophrenia

Some 50 years ago it was suggested that psychosis results from an imbalance in brain chemistry, with observations that hallucinogens such as lysergic acid diethylamide (LSD), and later amphetamine, psilocybine and mescaline and the more recent phencyclidine (PCP), could induce a schizophrenia-like state. The introduction of agents such as reserpine, which depletes central monoamines, and chlorpromazine, which blocks DA receptors, indicated that psychoses could also be treated by chemical means. A paradigm of hyperdopaminergic function in the schizophrenic brain soon took shape. Using neuroleptics radiolabelled with isotopes coupled with positron emission tomography (PET), investigators were not only able to demonstrate a high degree of binding to DA receptors by these agents, but were also able to visualise and measure the extent of binding, or occupancy, in the brain of human subjects. They found a strong correlation between potency in binding these receptors and response to the antipsychotic. However, while therapeutic levels of the classic neuroleptics correlate with high D_2 receptor binding, therapeutic levels of clozapine correlate strongly with binding to the D_4 receptor and less to the D_2 receptor.[9] Clearly, this pharmacological difference has clinical implications, since it becomes apparent that unlike the classic neuroleptics, clozapine was found to be effective in treating negative-symptom schizophrenia and also has a much lesser tendency to induce EPS. Clearly other mechanisms, exemplified by clozapine, could be explored for a more specific action against the symptoms of schizophrenia.

DA receptors are classed into two major families, viz. those that stimulate cyclic adenosine monophosphate (cAMP) synthesis as second messenger, namely the D_1 and D_5 receptors (termed D_1-like family), and those that either suppress or do not affect cAMP, namely the D_2, D_3 and D_4 receptors (termed D_2-like family.)[10-12] A discovery of great clinical value is that these DA receptors have also been found to be anatomically selective in their distribution and density in the brain. D_1 receptors are prominent in the cortical regions, D_2 receptors are prominent in the striatum while the D_3 and D_4 subtype of the D_2 family of receptors are expressed to a greater degree in the limbic regions of the brain.[12] Considering the source and distribution of dopaminergic pathways in the brain, there are three major DA projections. The nigrostriatal (NS) pathway, projecting from the substantia nigra, or A9 nuclei, of the midbrain to the caudate and putamen in the neostriatum (Fig. 1), is involved primarily in extrapyramidal motor functions.[13] In this context, it shares in a homeostatic regulatory role with GABA and Ach, which act via interneurons to regulate the behavioural actions of DA in the striatum.[14] The second

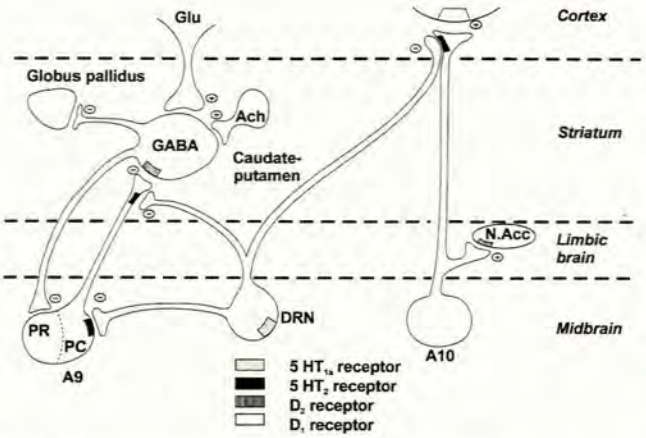

Fig. 1. Schematic representation of serotonergic-dopamine interactions in the striatum and prefrontal cortex. Serotonergic tracts from the DRN inhibit dopaminergic function at the DA cell body (A9 or substantia nigra) and at the end-synapses located in the caudate nucleus of the striatum through $5HT_2$ heteroreceptors. Similarly, serotonergic tracts innervating the cortex suppress D_1 receptor function in the limbic prefrontal cortex via $5HT_2$ heteroreceptors. 5HT function is regulated by somatodendritic $5HT_{1a}$ autoreceptors in the DRN. (Ach = acetylcholine; Glu = glutamate; GABA = gamma-aminobutyric acid; DRN = dorsal raphae nuclei; N Acc = nucleus accumbens; A10 = ventral tegmental nuclei; A9 = substantia nigra; PR = pars reticulata; PC = pars compacta.)

pathway, the mesocorticolimbic (MCL) tract, has two endpoints.[13] The first projection, originating from the ventral tegmental area (VTA) or A10 nuclei, innervates the limbic structures such as the nucleus accumbens, amygdylla, ventral hippocampus and prefrontal cortex (mesolimbic pathway; Fig. 1), and supports a variety of behavioural functions related to motivation and reward. This pathway is an important site of antipsychotic action against positive-symptom psychosis. The second A10 projection innervates the limbic cortex, e.g. the medial prefrontal, cingulate and entorhinal areas, and is involved in volition and affect (mesocortical pathway; Fig. 1). A third major DA tract, the tubero-infundibular projection (TIP), projects from the median eminence of the hypothalamus into the anterior lobe of the pituitary where it subserves neuro-endocrine functions, especially the control of prolactin secretion.[13] Consequently, non-selective block of both D_1-like and D_2-like families with a typical agent will not only induce a desired antipsychotic action through their action on mesolimbic D_3 and D_4 receptors, but will also induce a high incidence of EPS due to D_2 block in the striatum. Furthermore, unopposed D_1 block in the mesocortical pathway is associated with symptoms akin to negative-symptom schizophrenia known as 'neuroleptic-induced deficit syndrome'.[13] EPS predisposes to a more severe, possibly irreversible movement disorder, viz. TD. TD occurs in 20% of all patients who are on extended neuroleptic medication, and this can rise to 50% in the elderly.[15] Studies with clozapine have revealed that reducing the risk of

the more short-term EPS will lead to a similar reduction in reported incidence of TD. Excessive D_2 blockade in the TIP will result in varying neuro-endocrine abnormalities such as breast engorgement, gynaecomastia and other pituitary-mediated hormonal fluctuations.

DA and other neurotransmitter interactions as targets for antipsychotic action

D_2-selectivity

With the notable exception of clozapine, most traditional antipsychotic drugs block D_2 receptors in direct correlation to clinical potency.[11] However, there appears to be some differential sensitivity of the limbic and striatal D_2 receptors since high-potency (e.g. haloperidol) and low-potency (e.g. chlorpromazine) antipsychotics are equally effective in their respective dosage ranges, yet the latter are less prone to causing EPS. A threshold for EPS has now been observed with neuroleptics and can be used to predict with accuracy their cataleptic potential. Nyberg *et al.*[16] suggest that the threshold for antipsychotic action is a D_2 occupancy of 70%, with the D_2 threshold for EPS being 80%, although EPS may start to appear at striatal D_2 receptor occupancy levels of above 70%.[10,17] This response is directly related to blood levels. The suggestion is therefore that a dose-response curve for conventional neuroleptics needs to be established. One aim, then, of the 'ideal' antipsychotic has been to target the MCL DA neurons more selectively than those in the NS pathway in order to achieve a better ratio between limbic (antipsychotic) action versus NS (extrapyramidal) action. The archetypal group of antipsychotics that explore this benefit are the substituted benzamides, of which sulpiride is the only representative available in South Africa. Although the pharmacological profile of sulpiride suggests an atypical action, it fails to satisfy any of the prerequisites for atypicality, including low prolactin release and low EPS (Table I). Furthermore, few studies can validate the claims that sulpiride is effective for negative-symptom schizophrenia,[18] while those studies that have been performed indicate minimal efficacy and only if negative symptoms are not severe. Nevertheless, it would be valuable to discuss the pharmacology of sulpiride and why it fails to satisfy the criteria for an atypical antipsychotic. Like chlorpromazine, sulpiride is a low-potency D_2 antagonist that is superselective for the D_2 receptor, showing very little affinity for D_1 and D_5 receptors.[19] As with other benzamides, it also appears to act more specifically on the presynaptic D_2 autoreceptor.[20] Since nigral autoreceptors are predominantly of the D_2 type,[21] blocking of this auto-inhibitory receptor will increase DA release in the striatum, thereby reducing EPS. A similar facilitative action on prefrontal cortex DA function may occur, thereby improving negative symptoms. However, owing to its poor oral bio-availability (approximately 35%) and poor lipid solubility,[18] it requires extremely high doses for adequate antipsychotic action (600 - 1 800 mg/day).[19] This implies that there will be a high degree of binding to peripheral D_2 receptors, especially in the TIP, resulting in a high incidence of galactorrhoea and amenorrhoea.[19] Furthermore, these high doses will also impact on striatal D_2 receptors significantly enough to cause EPS (Table I).[18] In support of this, D_2 receptor occupancy has been found to be 78%.[18] Experience seems to emphasise that the drug is more useful in milder psychoses dominated by negative symptoms rather than more agitated conditions where positive symptoms predominate.[19] New, and possibly improved benzamides, such as amisulpride and raclopride, are at various stages of development.

D_1/D_2 balance

The neostriatum is rich in both D_2 and D_1 receptors, while the cortex expresses D_1 receptors in much higher levels than the D_2 receptor.[22] However, this apparently low level of D_2 receptor expression may still be important for antipsychotic actions, since chronic exposure to antipsychotics not only increases the level of D_2 receptors in the cerebral cortex, but also produces substantial downregulation of D_1 receptors.[22] This effect is possibly linked to sub-cellular receptor interaction between D_1 and D_2 receptor second messengers.[22] Deficits in cognitive

Table I. Limbic selectivity, D_2 occupancy and the dystonia-EPS potential of the new-generation antipsychotics

	A10:A9 selectivity?[30,31]	D_2 occupancy (%)	Dystonia-inducing dose (man)[19] (mg/d)	Therapeutic dose[19] (mg/d)	EPS potential
Sulpiride	NA	78[18]	2 000 - 8 000	600 - 1 800	++[18]
Risperidone	Slight	63 - 89[33,36]	5 - 20	4 - 16	0 to ++[15]
Clozapine	Yes	16 - 68[36]	< 1 500	100 - 800	0[15]
Olanzapine	Yes	43 - 89[36]	24 - 96	10 - 20	0[15]
Quetiapine	Yes	44[32]	1 200 - 4 800	300 - 900	0[37]
Ziprasidone	Yes	76[19]	NA	80 - 160	0 to +2[61]
Sertindole	Yes	NA	100 - 400	16 - 30	0[15]
Haloperidol	No	75 - 89[18]	5 - 20	5 - 20	+++[15]

0 = no difference v. placebo; + = mild; ++ = moderate; +++ = severe.

abilities are associated with cortical pathology, particularly frontal lobe lesions, and diminished D_1 stimulation has been found to result in diminished activity in prefrontal cortical neurons. Furthermore, it has been suggested that an abnormally low DA function in the prefrontal cortex of the schizophrenic brain sets the scene for a reactive increase in A10 DA activity resulting in an increase in mesolimbic DA function, thereby producing the ensuing positive symptoms of the disorder.[23] Hence a cortical site of action for the neuroleptics may be as important as a mesolimbic action. Lidow and colleagues,[22] however, suggest that there is an optimal balance between cortical D_1 agonism/antagonism as too much of either is associated with diminished cognitive functioning.

Although D_1 blockade alone appears to have limited antipsychotic action,[10,22] when combined with a traditional D_2 block possible improvements can be observed in therapeutic efficacy, and a decrease in EPS may be anticipated. The striatum, principal input structure of the basal ganglia, receives Glu stimulation from the cortex and responds through activation of a direct GABA-ergic and an indirect GABA-ergic innervation of the output stages of the basal ganglia, viz. the medial globus pallidus (Fig. 2).[24] The direct activation of descending GABA-ergic neurons innervates the medial globus pallidus, as well as the pars reticulata of the substantia nigra (Fig. 1), and is dependent on excitatory D_1 receptor activation. The activation of the descending indirect GABA pathway is mediated by inhibitory D_2 receptors on its cell body that activate a two-stage GABA inhibitory segment, through the lateral globus pallidus and then the subthalamic nuclei before activating the medial globus pallidus through an excitatory Glu pathway (Fig. 2).[24] Thus, DA exerts a differential action on these two pathways that effectively determines the degree of activation of the thalamic nuclei and its subsequent activation of the cortex. It is known that dyskinesias associated with DA agonists, such as L-dihydroxyphenylalanine (L-dopa) and bromocriptine, are due to their ability to create a neurological imbalance between these descending striatal D_1- and D_2-mediated pathways innervating the thalamus. Consequently, suppression of D_1-mediated activity coupled with D_2 stimulation, as in the case of bromocriptine, creates a relative imbalance in these two pathways resulting in less effective control over thalamic output, thereby inducing abnormal motor activity.[24] Contrary to bromocriptine, pergolide, a D_1/D_2 agonist, appears to be less prone to inducing dyskinesias and is more effective in reversing L-dopa-induced dyskinesia.[24] The reverse also applies, such that an imbalance in antagonistic actions on striatal D_1/D_2 activity may also lead to a greater prevalence of dyskinesias and EPS. Agents such as flupenthixol and zuclopenthixol, which combine approximately 80% D_2 occupancy and 15 - 35% D_1 occupancy, have demonstrated some minor clinical advantage.[19] However, where there is less of a difference between D_1 and D_2 antagonism, as with clozapine, olanzapine and ziprasidone, an improved EPS potential may become evident.

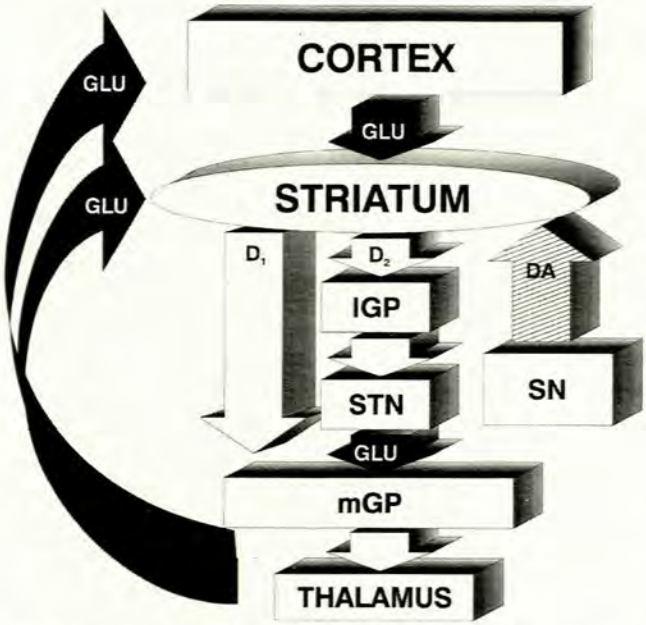

Fig. 2. Schematic representation of dopamine-GABA-glutamate interactions in thalamocortical-striatal circuits. (Refer to text for further discussion.) (Glu = glutamate; DA = dopamine; SN = substantia nigra; STN = subthalamic nucleus; IGP = lateral globus pallidus; mGP = medial globus pallidus. Glu pathways = black arrows; DA pathways = hatched arrows; GABA pathways = white arrows.)

D3 and D4 selectivity

Owing to the greater concentration of D_3 and D_4 receptors in the MCL tract,[12] select antagonism of these receptors together with less affinity for D_2 receptors present predominantly in the striatum, will allow for greater antipsychotic efficacy without paying a high cost in terms of EPS. However, the exact role of the D_4 receptor has been questioned,[25] and recent evidence, using a novel selective D_4 antagonist,[26] has revealed no obvious benefit in treating schizophrenia.[27] The D_3 receptor has also raised some interest,[28] although its exact role is uncertain due to there not being a select ligand available. It may prove to be the basis for the atypical action of sulpiride, which has a high affinity for this D_2 receptor subtype.[18,19] Select actions on limbic D_2 receptors, with minimal actions at striatal D_2 receptors, have distinct clinical value not only in the treatment of schizophrenia, but also in the treatment of dopaminergic-induced psychosis in Parkinson's disease, where striatal actions would be highly undesirable. Clozapine, olanzapine and risperidone have been found to be of value in these cases, without exacerbating parkinsonism.[29] Studies determining the differential inhibition of limbic A10 versus NS A9 neurons indicate that mesolimbic A10 selectivity is achieved with clozapine, quetiapine, olanzapine, ziprasidone and sertindole and to a lesser degree with risperidone (Table I).[30,31]

5HT/DA balance

It is well documented that serotonergic agents, such as the selective 5HT re-uptake inhibitors, may induce or exacerbate EPS, while $5HT_2$ antagonists can alleviate or prevent it.[12] Serotonergic projections from the dorsal raphae nuclei project to the substantia nigra where they act on somatodendritic $5HT_2$ heteroreceptors on dopaminergic neurons to inhibit their firing (Fig. 1).[12] Similarly, serotonergic projections from the dorsal raphae project via the median forebrain bundle to the striatum and cortex, to inhibit neuronal firing by decreasing synthesis and/or release of DA. As can be expected, lesioning these 5HT pathways will cause a disinhibition of DA neurons and an increase in DA levels.[12] $5HT_{1a}$ agonists will effectively reduce serotonergic outflow, thereby attenuating post-synaptic $5HT_2$ receptor function in the SN and striatum.[12] This action effectively disinhibits DA function. The $5HT_{2c}$ receptor also appears to play a role in the genesis of psychosis, since agonists at this receptor can exacerbate the positive symptoms of schizophrenia.[32] Both 5HT and DA tracts converge in the ventrolateral nucleus accumbens, suggesting a dual role in psychotic behaviour.[33] LSD exerts its hallucinogenic effect through stimulation of the $5HT_2$ receptor.[13] While the clinical relevance of these effects is uncertain, $5HT_{2c}$ antagonism may contribute to antipsychotic action.[34]

Since D_1 and D_2 receptor blockade may be facilitated or augmented in the forebrain and midbrain areas by 5HT, antipsychotics with inherent $5HT_2$ receptor-blocking action or $5HT_{1a}$ presynaptic autoreceptor agonist activity will allow disinhibition of the D_2 receptors in the striatum, thereby alleviating neuroleptic-induced EPS. Such a drug may have further therapeutic advantages, although recent studies refute this supposition.[35,36] The negative symptoms of schizophrenia, including anhedonia, apathy, blunted affect, and poverty of speech, respond with great difficulty to typical antipsychotics, and many patients freed from their delusions and hallucinations are still unable to resume productive lives because of enduring negative symptoms. Evidence is that these symptoms reflect, in part, hypodopaminergic D_1 receptor function in the prefrontal cortex.[22] Clozapine may act to increase DA in the prefrontal cortex by stimulation of presynaptic $5HT_{1a}$ autoreceptors.[37] Furthermore, these effects on $5HT_{1a}$ and $5HT_2$ receptors may also constitute an antidepressant-like action,[13] which may contribute to their efficacy against negative symptoms. Atypical agents have been associated with induction of mania.[38,39] Drugs with prominent $5HT_2$ receptor inhibition include most of the new atypical agents, viz. clozapine, olanzapine, risperidone, ziprasidone, quetiapine and sertindole. Recently, 5HT receptors specific for the striatum, viz. $5HT_6$, and hypothalamus and limbic areas, viz. $5HT_7$, have been identified, and may have significance in future drug development.[30] A disadvantage of $5HT_2$ block is its association with weight gain. However, evidence suggests that weight gain on psychotropics may be more pronounced with agents with combined $5HT_2$ and H_1 receptor antagonism than with either of these agents alone.[40] As such, clozapine, olanzapine and quetiapine will induce this side-effect to a greater degree.

DA/Ach balance

Designing an antipsychotic drug with a strong antimuscarinic action may counter the cortical-striatal DA/Ach imbalance induced by the powerful D_2 block that underlies movement abnormalities seen in Parkinson's disease and iatrogenic parkinsonism (Fig. 1).[14] This, however, would also confer a higher incidence of typical anticholinergic side-effects that may be troublesome to the patient. Furthermore, a theory of cholinergic hyperactivity has been suggested as a basis for negative symptoms,[41] suggesting a possible benefit of anticholinergic action in negative-symptom schizophrenia. Agents that may utilise these benefits would include clozapine and olanzapine; in addition preliminary evidence suggests that both clozapine[42] and olanzapine[43] have distinct benefits in terms of improving cognition. The mechanisms of this response are undefined at present, and in fact appear paradoxical. The cognitive impairment typical of Alzheimer's disease (AD) appears to be strongly associated with diminished cholinergic function, thus raising the question of how an anticholinergic property would benefit the cognitive impairment seen in negative schizophrenia. The improvement in cognition observed with the above two agents may occur secondary to improved EPS, improvement in negative symptoms or through another more complex mechanism. Furthermore, cholinergic agonists produce only limited improvement in AD,[13] thus implicating additional pathways in memory and cognitive function. Hippocampal Glu pathways are strongly implicated in memory formation, with Glu hypofunction associated with memory loss and diminished cognitive function.[13] Distinct diminution in Glu function has been observed in the hippocampus and cortex of schizophrenics (see following section). A recent study indicates that administration of the non-competitive antagonist of the NMDA subtype of Glu receptor, PCP, results in DA dysfunction in the dorsolateral prefrontal cortex and is accompanied by distinct cognitive deficits.[44] A role for Ach is possible in this context since Ach exercises a permissive action in Glu-induced neuronal excitotoxicity.[45] The neurotoxic action of Glu, resulting in death of Glu neurones, can be inhibited by anticholinergic agents,[46] suggesting that an additional anticholinergic action may be advantageous in addressing negative symptomology and in preventing the longitudinal deterioration, including refractoriness and relapse,[45] so often observed in schizophrenic patients.

GABA/Glu balance

The striatal complex, comprising the striatum and globus pallidus, is under inhibitory control of the NS DA pathway, and under stimulatory control of the glutamatergic pathway

from the cortex and thalamus (Figs 1 and 2).[47] This balance of power maintains an inhibitory GABA-ergic action on the thalamus leading to a reduced transmission of sensory information to the cerebral cortex. However, any condition causing a loss of or diminished Glu tone would be equivalent to an elevated DA tone, namely insufficient suppression of the thalamic output to the cortex causing hyperarousal, confusion and psychosis.[47] There is significant evidence implicating Glu hypofunction in the chemical pathology of schizophrenia. PCP and ketamine, two dissociative anaesthetics, are psychotomimetic by virtue of their ability to block the NMDA receptor.[46] Furthermore, the principal second messengers induced by NMDA activation, viz. Ca^{2+}, nitric oxide and cyclic GMP, are also modified by antipsychotic medication.[45] Prolonged NMDA hypofunction also results in limbic and neocortical neuronal damage not unlike that seen in the schizophrenic brain.[46] Hypofunctional Glu receptors ultimately impact on GABA transmission, resulting in impaired GABA control over corticolimbic neurons. An initial excitotoxic insult early in development may destroy either the NMDA receptors, or the GABA neurons expressing these receptors, resulting in an unopposed disinhibition of unmodulated stimulatory activity that floods corticolimbic brain regions. Such a lesion is asymptomatic in the developing fetal brain. However, these damaged circuits may be recruited in early adolescence, with the ensuing presentation of psychotic symptoms, and may later lead to ongoing structural damage. Studies done on rat pups have demonstrated an age-related sensitivity to NMDA antagonists, where the animals are resistant to the neurotoxic effects of MK-801, but become sensitive after puberty.[46] In man, an analogous result using ketamine has demonstrated the relative lack of psychotogenic effects of ketamine in pre-adolescent children, with these effects becoming prominent in adolescents and adults.[46]

Further supportive evidence for *in utero* excitotoxic cell death comes from the consistent neuropathological finding that gliosis is absent in the schizophrenic brain, in spite of the apparent neurodegenerative profile of the disorder (viz. cortical volume loss, enlarged ventricles). Gliosis is an associated finding in most neurodegenerative diseases, e.g. Alzheimer's disease and Parkinson's disease, but is not found in neurodegenerative disorders that occur early in brain development.[48] In addition, cyto-architecture studies done on the schizophrenic brain indicate that there is a laminar distribution of cortical neurons inwards. This implies that the neurons destined for the cerebral cortex, which normally proceed outwards from the periventricular sheath of the neural tube, have died off and therefore not reached their intended destination.[48] Neuropsychological studies also support an early-onset brain abnormality. Children who will later develop schizophrenia have been found to have distinct neuromotor and neuropsychological deficits in early childhood before any psychiatric symptoms appear.[48] The actions on Glu function by the agents discussed in this review have not been fully explored, although it is anticipated that some of the newer drugs, such as D-cycloserine, will exploit this mechanism. A recent study[49] suggesting a role for agonists at the presynaptic auto-inhibitory metabotropic subtype of the Glu receptor may also represent a novel non-DA approach to the treatment of schizophrenia. The multi-receptor antagonists clozapine, quetiapine and olanzapine have been shown to antagonise the behavioural effects of Glu-NMDA receptor antagonists such as phencyclidine and MK-801.[42,50] While these data support the Glu hypofunction hypothesis of schizophrenia, Swerdlow *et al.*[50] found that haloperidol and risperidone were devoid of this ability, such that the full implication in the treatment of the disorder remains speculative at present.

'Atypical' new-generation antipsychotics

While there are many experimental agents at various stages of clinical development, we will be focusing specifically on those atypical agents already available in South Africa, or that may

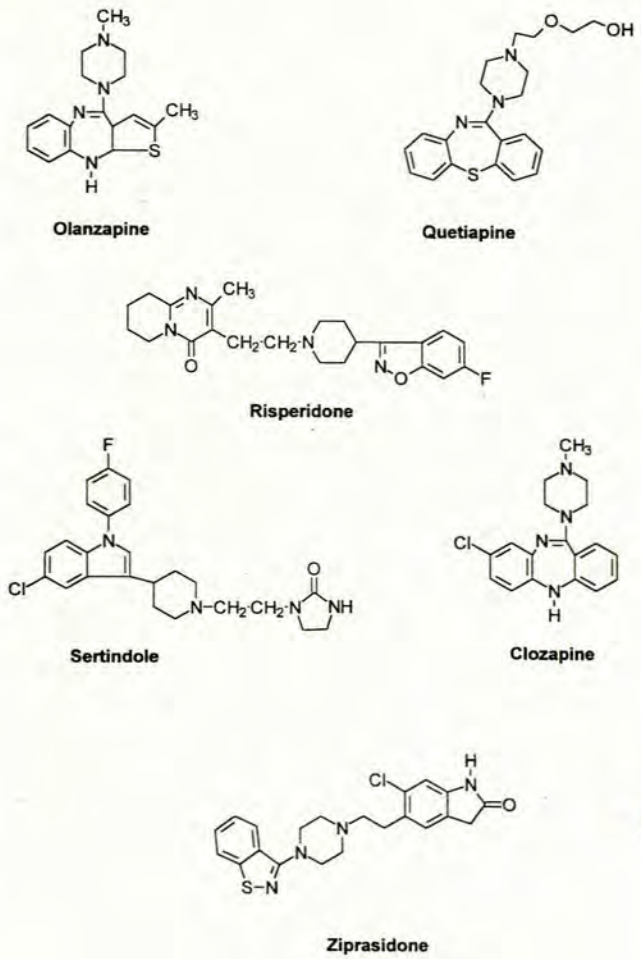

Fig. 3. Structural formula for the new-generation atypical antipsychotics.

be introduced in the near future. These include clozapine, risperidone and olanzapine (already available), sertindole and quetiapine (available elsewhere, e.g. the USA and Europe), and ziprasidone, which is in late-stage development. Their chemical structures are depicted in Fig. 3.

Serotonin-dopamine antagonists

Risperidone (Risperdal; Janssen-Cilag)

This agent was developed following observations that the selective $5HT_2$ antagonist, ritanserin, improved negative symptoms and reduced EPS when combined with haloperidol.[51] Risperidone is a high-potency antipsychotic belonging to the benzisoxazol family. It offers greater $5HT_{2a}$ antagonism relative to D_2 receptors,[52] a profile which, as predicted by the 5HT/DA balance theory discussed above, should afford it a low risk of EPS. At doses at the lower end of its dosage range (< 6 mg/day), few EPS are experienced and its efficacy against negative symptoms and occurrence of EPS is markedly superior to that of 20 mg/d haloperidol. Single-dose PET studies using subclinical dosages of 1 mg reveal 50% occupancy of both $5HT_2$ and D_2 receptors.[52] Since this response is dose-dependent, it can be predicted that higher occupancy will occur at its clinically relevant doses. Recent PET studies have therefore revealed a high degree of D_2 occupancy in the striatum at a 6 mg/day dosage, viz. 75 - 80%[53] and over a 2 - 12 mg/day dose range, viz. 63 - 89%.[36] Since risperidone has no inherent antimuscarinic activity, its low EPS profile is most likely linked to its potent $5HT_2$ antagonistic property,[54] allowing for DA disinhibition in the striatum and prefrontal cortex. However, its cataleptic and therapeutic dosages are in the same range (Table I) such that this mechanism alone appears not to be enough to prevent EPS. Dosages higher than 10 mg/day are associated with an increasing incidence of EPS,[19] while neuroleptic malignant syndrome (NMS) has also been associated with its use.[55] Nevertheless, risperidone, in recommended dosages, viz. 2 - 6 mg/day, is highly effective against both positive- and negative- symptom schizophrenia, causing fewer EPS than the conventional neuroleptics.[2]

Daily dosages in excess of 10 mg do not appear to offer any added therapeutic benefit.[51] In fact, in the higher-dosage groups (12 - 16 mg), the therapeutic effect is lower than that produced by 4 - 8 mg, suggesting that a bell-shaped response emerges for the therapeutic effect as a function of dose.[54] There is evidence for a faster onset of action compared with typical agents,[56] and it appears more effective than these latter agents in managing refractory schizophrenia.[3,4] In addition, risperidone is finding favour in the treatment of other conditions, such as psychosis in the elderly[8] and mania.[57] Continuation studies have revealed that the drug maintains its response beyond the 8-week double-blind period,[2] and that it is well tolerated and effective in long-term treatment.[51,56] A study comparing it with clozapine in acute schizophrenia revealed no significant difference,[51] while studies in refractory patients similarly reveal equal efficacy.[4,58] Risperidone presents with a significant degree of alpha-1 adrenoceptor block, resulting in sedation, orthostatic hypotension and cardiac palpitations. For these reasons, titration of risperidone dosage is recommended.[56] Due to powerful $5HT_2$ antagonism, weight gain can be anticipated,[56] while a marked increase in prolactin is also seen.[19] Although the clinical relevance is uncertain at this time, risperidone also has a high affinity for the $5HT_7$ receptor.[59]

Ziprasidone (Zeldox; Pfizer)

Ziprasidone is a medium-potency benzisothiazoyl piperazine still in late-phase clinical trials. It has a purported dosage range of 80 - 160 mg per day. The receptor binding of ziprasidone is similar to risperidone, yet it is also unique, binding significantly to D_2-family receptors such as D_3 and D_4, but not D_1 receptors.[8,34] Ziprasidone binds to a great many 5HT receptor subtypes, including $5HT_{2a}$, $5HT_{2c}$, $5HT_{1a}$ and $5HT_{1d}$.[34] Affinity for the $5HT_{1a}$ receptor may be associated with anxiolytic effects.[60] Since $5HT_{2c}$ antagonism may contribute to antipsychotic effects, this property may contribute to its clinical efficacy.[34] It has a moderate affinity for the alpha-1 adrenoceptor and the H_1 receptor, while its affinity for alpha-2 receptors and muscarinic receptors is negligible.[8,34] Ziprasidone presents with a limbic-selective action[31] and it displays the highest $5HT_2/D_2$ ratio among the new agents, being twice that observed with clozapine.[34] Early clinical trials indicate comparable efficacy with haloperidol at dosages of 120 mg/day.[2,19] However, single-dose PET studies with a subclinical dose of 40 mg and 60 mg demonstrate striatal D_2 receptor occupancies of 77% and 82%, respectively,[34,61] accompanied by a robust elevation in prolactin release.[19,61] These observations predict a relative risk for EPS that may be dose-related. As with risperidone, its potent $5HT_2$ antagonism will work to its advantage, provided dosages are not excessive. The clinical profile,[8] therefore, reveals an agent that has both positive and negative symptom efficacy, with a favourable motor side-effect profile,[8] with little to no parkinsonism and akathisia noted. Side-effects are also relatively predictable given its receptor-binding profile, and include prolactin release, sedation, headache, agitation and orthostatic hypotension.[19] No cardiac, haematological and hepatic changes have been noted, while, possibly because of a low H1- binding, weight gain appears to be less of a problem with this agent.[8]

Sertindole (Serlect/Serdolect; Lundbeck)

Sertindole, a phenylindole derivative, is a high-potency product with a dosage range of 8 - 24 mg/day. It, too, may be tentatively grouped as a '$5HT_2/D_2$/alpha-1 antagonist', along with ziprasidone and risperidone. However, it differs slightly in that its D_2 affinity is markedly higher than that of its comparators.[62] This would have impacted heavily on EPS had it not also demonstrated the highest $5HT_2$ antagonism in the

group.[62] D_2 receptor occupancy studies reveal significantly lower striatal D_2 binding compared with haloperidol, but significantly higher binding than clozapine.[63] Nevertheless, sertindole has an estimated dystonia-inducing dosage in man of 100 - 400 mg/day, much higher than its therapeutic dosage range (Table I),[19] such that EPS is expected to be very low. Furthermore, it inhibits VTA DA activity at doses 100-fold less than those needed to inhibit SN DA activity. Clinical trial data indicate that sertindole produces motor side-effects indistinguishable from placebo, both for parkinsonism and akathisia.[8] The drug lacks affinity for the D_1 receptor family, while its limited action on H_1 and muscarinic receptors[8] suggests a low incidence of sedation, dry mouth, etc. Due to its powerful alpha-1 block, side-effects include headache, nasal congestion and diminished ejaculatory volume, while insomnia is also reported. Prolongation of the QT interval[15,64,65] may occur, although these ECG changes have not been related to clinical signs or symptoms, e.g. syncope, arrhythmias.[64,65] There appears to be a low risk of seizures with sertindole,[15] as well as no evidence for significant liver dysfunction or agranulocytosis.[64] A recent clinical trial comparing sertindole with haloperidol revealed comparable efficacy in treating psychosis. Dosages at the upper end of its range (20 mg/day) were found to be superior to placebo in addressing negative symptoms.[65] Its apparent superiority in this regard over haloperidol became noticeable after week 8 when the haloperidol response on negative symptoms appeared to plateau.[65] A path analysis revealed a significant effect of the drug on negative symptoms.[8] At all doses, haloperidol produced significantly more EPS, with EPS for sertindole being indistinguishable from placebo. Sertindole-treated patients remained free of hospitalisation and medically compliant for significantly longer periods of time than those on haloperidol.[66] There is also preliminary evidence to suggest efficacy in treatment of refractory psychosis.[67] Sertindole may be comparable to clozapine in terms of managing partially responsive schizophrenics.[68]

Multireceptor antagonists

Clozapine (Leponex; Novartis)

Clozapine, a dibenzodiazepine, is the archetypal atypical antipsychotic, and is the agent for which the most is known. It is referred to as a multireceptor antagonist, having significant affinity for D_1, D_2, $5HT_2$, alpha-1, muscarinic and histamine-H_1 receptors. It has a high affinity for the alpha-2 receptor, which suggests a tentative role for this receptor in the atypical nature of clozapine.[69] The exact explanation for its atypical nature is still the subject of speculation, although it may include a number of the latest theories discussed earlier.

Significant efficacy on negative symptoms has been ascribed to its antimuscarinic actions, alpha-2 antagonism, high $5HT_2/D_2$ ratio allowing D_1 receptor disinhibition and/or its mesolimbic-specific action via D_4 receptor antagonism.

Clozapine presents with a high $5HT_2/D_2$ ratio[62] and a well-established reputation for inducing few to no EPS. In addition, its high antimuscarinic action, favourable D_1/D_2 antagonism ratio and an extremely low occupancy of striatal D_2 receptors, viz. 16 - 68% over a dose range of 75 - 900 mg/day[36] may contribute to this clinical profile. Clozapine has an estimated dystonia-inducing dosage in man of 1 500 mg/day compared with its therapeutic range of 200 - 600 mg/day. It has, therefore, a markedly lower risk of causing acute and chronic EPS, such as akathisia and TD. It also has a unique binding profile to the $5HT_6$ and $5HT_7$ receptors present in the striatum and the limbic and hypothalamic areas, respectively, allowing more specific targeting of 5HT effects on DA actions in these areas.[30,59] Affinity for the $5HT_{2c}$ receptor may confer benefit for positive symptom management.[34] Numerous studies have proved that clozapine has an antipsychotic effect equal to or better than that of the typical antipsychotics, with significantly better efficacy in treating positive and negative symptoms.[19] Superior benefits have also been noted with regard to its ability to address cognitive impairment[43] as well as the general psychopathology of schizophrenia, viz. anxiety, depression and hostility. It is also superior in its ability to increase social functioning, work capabilities and quality of life[19] and it can reduce the risk of suicide.[19] Outcome studies have clearly indicated its ability to reduce hospitalisation, with 17% of clozapine patients versus 32% on conventional antipsychotics requiring hospitalisation after 1 year.[1] Clozapine has been used with success in schizo-affective and bipolar disorders, while it also has value in treating severe TD or tardive dystonia.[52] However, despite these unquestionable benefits, clozapine has a 1% risk of causing potentially fatal agranulocytosis,[70] possibly associated with greater age and female gender.[51] There may be a genetic link as well as an immune component to this adverse event.[51] It is therefore normally restricted to treatment-resistant patients who have failed to respond to two or more traditional antipsychotics, where it has a success rate of 30 - 50%, and for patients with unmanageable EPS and TD. Because of its low potency (dosage range of 200 - 600 mg/day), the high doses required for its therapeutic effect will allow a high degree of binding to other receptors, resulting in a variety of autonomic side-effects, e.g. sedation and postural hypotension.[19] Due to its high affinity for the H_1 receptor, and coupled with its potent $5HT_2$ antagonism, problems with weight can be a major complicating factor as far as compliance is concerned. A unique property of clozapine is its selective agonist activity on the muscarinic M_4 receptor,[71] as well as alpha-2 antagonism,[69] which may be responsible for the high incidence of troublesome hypersalivation that this agent causes.[62,70] Clozapine also has a high risk of inducing seizures in susceptible individuals, although there is a lower risk than with the older typical agents. It is clearly dose-related, with the incidence rising from 1% (300 mg/d) to 2.7% at 300 - 600 mg/d and 4.4% for dosages in excess of 600 mg/d.[15] Despite nearly 25

years of clinical use, there is still uncertainty regarding the dosage range of this compound.[2] Dose titration, however, is critical at the start of treatment.[51]

Olanzapine (Zyprexa; Eli Lilly)

Olanzapine is a high-potency analogue of clozapine, with a similar chemical structure (Fig. 3), and a similar pharmacology. Chemically it is termed a thienobenzodiazepine. Olanzapine is, therefore, a multireceptor antagonist with considerable affinity for D_1, D_2, $5HT_2$, histamine H_1, alpha-1 and muscarinic M_1 receptors.[70] Despite its potential to influence many receptors, its high potency allows it a more select action on the required DA and 5HT receptors without bringing about a heavy side-effect burden.[30] While anticholinergic side-effects are evident, they are usually low (< 15%).[70] It presents with the highest antimuscarinic action of the group,[62] an effect that may be valuable in preventing the longitudinal cognitive deterioration observed in schizophrenic patients.[41,42] Its low but significant action on glutamate receptors[30,42] may also have a role to play in improving long-term outcome. Olanzapine also binds strongly to the newly identified $5HT_6$ receptor that has a high density in the striatum, a profile that may well have a significant role to play in allowing DA disinhibition in the striatum.[70] Olanzapine, similarly, has a high affinity for the limbic D_4 receptor, while PET studies indicate a single 10 mg dose D_2 occupancy in the striatum to be 59 - 63%,[72] although a dose ranging study (5 - 60 mg) revealed 43 - 89% D_2 occupancy.[36] Consequently, as evinced from studies evaluating its dystonia potential in man, viz. 24 - 96 mg/day, versus its nominal dosage range of 10 - 20 mg/day (Table I), it will have a low tendency to induce EPS within its recommended dosage range.[15] Dual D_1/D_2 antagonism may also contribute here. This prediction of low motor side-effects has been borne out in clinical trials,[70] although akathisia[73] as well as NMS[74] have been noted. Unlike clozapine, olanzapine has little to no affinity for the alpha-2 and $5HT_7$ receptor.[70] Furthermore, it may induce a transient but clinically irrelevant elevation of prolactin.[75] Significant $5HT_2/H_1$-blocking activity predicts that weight gain will be a detrimental factor in therapy. Treatment with olanzapine may be associated with a transient elevation in the levels of hepatic transaminases, viz. alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase. However, no clinical symptoms of hepatotoxicity were noted.[70] Bearing in mind its close structural similarity to clozapine, the most crucial question relates to the relative risk of developing agranulocytosis. So far there have been no reports of granulocytopenia, including reports of 32 patients who had previously experienced clozapine-induced agranulocytosis and/or neutropenia and who switched to olanzapine.[70] Olanzapine appears to have a relatively low risk of inducing seizures.[15] Placebo- and haloperidol-controlled studies have revealed the efficacy of olanzapine with regard to both positive and negative symptoms of schizophrenia, with greater improvements in negative symptoms compared with haloperidol.[70] In addition, the agent also appears to have a relatively rapid onset of action, with a response greater than placebo evident within 1 - 2 weeks.[8,70] A path analysis of the clinical trial data reveals that olanzapine exerts a direct influence on primary as well as secondary negative features.[76] As a result, overall quality of life is improved and there is a significantly higher probability of maintaining a response over long-term treatment compared with haloperidol.[1,70] Olanzapine demonstrates efficacy in schizophreniform disorders and schizo-affective disorder[77] as well as bipolar disorder.[78] Interesting results from a recent double-blind comparison between olanzapine and risperidone in the same group of patients[79] provide evidence that olanzapine is superior in negative symptom efficacy and tolerability as well as in its ability to maintain a clinical response over time. However, this trial did not use doses of comparable D_2 occupancy[36] and therefore comparisons should be interpreted with caution. Although preliminary case reports reveal efficacy at dosages exceeding 20 mg/day,[80] efficacy in resistant schizophrenia still needs to be assessed definitively. A double-blind study comparing olanzapine (22 mg ± 3.4 mg/day) to clozapine (354 ± 146 mg/day) provides evidence that olanzapine is at least as effective as clozapine in treating resistant schizophrenia.[81] This latter study, however, requires confirmation.

Quetiapine (Serequel; Zeneca)

Quetiapine, a dibenzothiazepine, is structurally similar to clozapine and olanzapine (Fig. 3) and also acts as a multi-receptor antagonist. However, it appears to have greater alpha-1 blocking action, with less potent D_2 and $5HT_2$ antagonism, slight D_1 blocking activity and minimal activity at muscarinic-cholinergic receptors.[2] Quetiapine also demonstrates moderate 5HT and noradrenaline re-uptake blocking properties.[8] It is a low-potency agent (300 - 900 mg/day), with an estimated dystonia-inducing dosage in man of between 1 200 and 4 800 mg/day.[19] It demonstrates dose selectivity for the A10 DA neurons in chronic treatment.[8] A dose of 450 mg results in 44% striatal D_2 occupancy,[82] suggestive of a low EPS potential, as well as a low tendency to induce prolactin secretion. This has been validated in clinical trials,[83,84] where little to no EPS or elevated prolactin release was noted.[85] The drug also shows promise in the treatment of DA agonist-induced psychosis in patients with Parkinson's diseases, without exacerbating parkinsonism.[86] Quetiapine produces decrements in both positive and negative symptoms in schizophrenia, and appears to have similar efficacy to traditional antispychotics,[84] although efficacy in treating negative symptoms appears to be less consistent.[2,8,83] As can be predicted from its multi-potent receptor profile, common side-effects include sedation, insomnia, postural hypotension, agitation and dry mouth,[19] as well as weight gain.[83] Transient elevation in liver enzymes, a reduction in thyroxine T4 levels[83] and transient neutropenia have been noted.[2] Considering the decreased T_4, there is no evidence for an increase in thyroid-stimulating hormone or of

clinical hypothyroidism.[83] No effects on haematological and electrocardiographic parameters and prolactin have been noted.[83]

CONCLUSION

This paper reviewed the most recent pharmacological agents for schizophrenia and discussed their characteristics in the light of new work on the neurobiology of schizophrenia. Although there are a number of theories that may be applied to the development of the atypical antipsychotic, the theory most exploited in these new drugs, and therefore of greatest value in explaining their atypical action, is their superior $5HT_2$ antagonism over D_2 antagonism. One might speculate that DA antagonism accounts for the proximal antipsychotic effects, while 5HT antagonism may be more beneficial for ancillary symptoms and more distal outcomes, such as improved functional status and quality of life. The addition of D_3 or D_4 antagonism, muscarinic antagonism, alpha-2 antagonism, balanced D_1/D_2 antagonism and effects on Glu, as seen with the multireceptor antagonists, may allow the mustering of a greater clinical response with a lower D_2 occupancy, thereby allowing equal efficacy at lower doses and therefore less risk of EPS.[36] Certainly, agents with any one of these properties alone do not appear to be effective antipsychotics. Whether $5HT_2/D_2$ balanced antagonism can be excluded in the light of newer strategies, such as Glu antagonism or partial D_2 antagonism, will no doubt be evaluated in time.

The true value of these new atypical antipsychotics, their ability to address adequately all the symptoms of schizophrenia, namely to reduce long-term cognitive impairment, to reduce hospitalisation and to allow maximal reintegration of these patients into society, will only be borne out over time. All the agents have demonstrated efficacy in treating positive symptoms comparable with conventional antipsychotics, while also demonstrating marked improvement in EPS profiles. There is also evidence for efficacy in addressing negative symptoms. However, their efficacy in this regard compared with the atypical reference drug, clozapine, needs to be assessed urgently. Exploration studies with these agents in pre-adolescent children are also needed.[87]

Since it became available in the 1970s, the benefit of clozapine has been without question. The pharmacological aspects of this multi-potent drug, and the characteristics of the ideal antipsychotic, still remain locked in our lack of understanding of an extremely complex disorder. Nevertheless, the new antipsychotics appear to have several distinct advantages over earlier agents. Their more favourable side-effect profile is likely to improve patient compliance. This, together with improved efficacy across a broader range of symptoms, should result in a better outcome, and an improved quality of life for patients suffering from schizophrenia.

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