Atypical neuroleptics

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The discovery that clozapine alleviates both positive and negative symptoms of schizophrenia has resulted in the emergence of newer atypical neuroleptics. Even though they are more expensive than traditional antipsychotics they have distinct and important advantages, which may influence the extent of the patient's rehabilitation and compliance.

If the introduction of chlorpromazine liberated psychotic patients from straitjackets in the middle of this century, the newer atypical neuroleptics are probably going to ensure better quality of life for patients in the community, by diminishing substantially the distress caused by extrapyramidal side-effects (EPS) and improving the mood and negative symptoms of schizophrenia.

For the last four decades, the main treatment of schizophrenia has relied on the blockage of dopamine D_2 receptors. Classical antipsychotics such as chlorpromazine and haloperidol are powerful in reducing the positive symptoms (delusions, conceptual disorganizations, hallucinations) but they have negligible effect in improving negative symptoms (apathy, loss of drive, slowness, social withdrawal).

PROBLEMS OF SIDE EFFECTS

All the conventional neuroleptics inhibit both the ventral tegmental and substantia nigra dopaminergic neurons, thereby causing EPS as well as antipsychotic actions. The classical antipsychotics have several unwanted side-effects, poor effects on negative symptoms and inadequate response in some patients, known as neuroleptic non-responders. Acute EPS (Parkinsonism, akathisia, dystonia), tardive dyskinesia, weight gain, hormonal and sexual effects (e.g. galactorrhoea, impotence, ejaculatory dysfunction), sedation, postural hypotension and autonomic effects have caused obvious limitations for these drugs.

With standard antipsychotic agents at least 30% of schizophrenic patients exhibit an inadequate or poor response (Kane, 1989), and in addition nearly 60% of patients relapse after 1 year of therapy (Kane, 1996). Parkinsonism can occur in up to 40% of patients taking standard neuroleptic drugs (Barnes, 1992). Akathisia occurs in 25–75% of patients receiving traditional neuroleptics (Braude et al, 1983; Van Putten et al, 1984; Sachdev and Kruk, 1994). Dystonia typically occurs in 2.5–5% of patients taking conventional neuroleptics but it occurs up to 25% of high risk patients which include young males (Rupniak et al, 1986; Simpson and Singh, 1989).

The average prevalence of tardive dyskinesia is 20% in patients exposed to a standard neuroleptic for over 3 months and after 25 years exposure the incidence increases to 70% (Woerner et al, 1991; Latimer, 1995). Patients with affective disorder, in particular major depression, appear to run a higher risk of developing tardive dyskinesia (Cavallaro and Smeraldi, 1995). EPS can lead to important management problems and distressing social stigma.

Two of the major barriers to compliance are unpleasant and long-standing EPS as well as patients lacking insight into their abnormal mental state (Kerwin, 1996). In a review of 12 studies of factors affecting compliance with antipsychotic medication among outpatients with schizophrenia, 11 studies found a positive association between EPS and non-compliance (Young et al, 1986). EPS often remain untreated because little can be done to reduce them. Acute EPS can be treated with an anticholinergic drug but this will only reduce the occurrence of EPS by up to 50% (Gerlach and Peacock, 1995).

In recent years, the most important breakthrough in the treatment of schizophrenia has been the discovery that clozapine not only alleviated the positive symptoms, but also the

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negative schizophrenic symptoms. EPS characteristic of typical antipsychotics have been found to be absent in clozapine-treated patients. These findings paved the way for the emergence of newer atypical neuroleptics promising a possible new dawn in biological psychiatry.

ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics were originally distinguished from classical antipsychotics by their ability to discriminate between animal models predictive of antipsychotic action and EPS. They do not produce catalepsy in rats. They have greater efficacy against negative symptoms, greater efficacy against mood symptoms, very favourable EPS profiles and negligible effects on prolactin levels. The hypothalamic–pituitary axis is innervated by dopaminergic receptors, which have an inhibitory effect on the release of prolactin. Conventional antipsychotic drugs block this inhibition, resulting in the elevation of prolactin level which can lead to galactorrhoea and sexual dysfunction.

The atypical antipsychotics inhibit the dopaminergic transmission responsible for antipsychotic effect by blocking 5-hydroxytryptamine $(5HT)_{2A}$ receptors in the ventral tegmental area of the brain. Atypical neuroleptics do not apparently affect dopaminergic transmission in the substantia nigra and therefore are less likely to cause EPS. The atypical antipsychotics affect the serotonin receptor function in the frontal cortex, leading to an improvement in negative symptoms. The mechanism of this action is still unknown.

The recent findings that specific serotonin-reuptake inhibitors (SSRIs) can improve negative symptoms while having little effect on dopamine receptors support the involvement of the serotonergic system in this activity. However, reduction in cognitive impairment and absence of EPS could alone explain the apparent reduction of negative symptoms. It is now agreed that both serotonergic and dopaminergic systems are critical to the pathophysiology of schizophrenia. Although clozapine may have undermined the dopamine hypothesis of schizophrenia, dopamine is still the main neurotransmitter of schizophrenia. Some have suggested that serotonergic pathways may be responsible for the negative symptoms.

Atypical antipsychotics originally included sulpiride, thioridazine and loxapine. The newer atypical antipsychotics fall broadly into two groups:

1. $5HT_2$, D_2 receptor blockade drugs
2. Multiple receptor affinity drugs with relatively poor affinity for D_2 receptors. The recently introduced amisulpiride is a D_2, D_3 receptor blockade drug.

Risperidone, sertindole, ziprasidone and aripiprazole belong to the first group, whereas clozapine, olanzapine, quetiapine and zotepine belong to the second group.

Risperidone

Risperidone is a potent D_2 receptor antagonist. It has a regional preference for blocking D_2 receptors in the mesolimbic cortical bundle. It is a potent $5HT_2$ receptor antagonist, α-adrenergic receptor and histamine-H_1 receptor antagonist. It has fewer EPS at doses up to and including 5 mg twice daily. At a dose of 6 mg daily, the incidence of EPS is no greater than placebo (Peuskens, 1995). Risperidone in recommended doses is generally very well tolerated compared with clozapine and conventional drugs (Thomas and Lewis, 1998). The consensus seems to be that a dose of 4 mg daily may be effective, particularly for first episode patients (Kopal, 1996).

When compared with other antipsychotic drugs, more akathisia is observed. Postural hypotension is a side effect. The starting dose should be 1 mg twice daily which is then increased over 3 days to 3 mg twice daily. Doses of risperidone greater than 10 mg increases the risk of EPS (Association of the British Pharmaceutical Industry, 1998). Risperidone has been associated with at least 10 cases of neuroleptic malignant syndrome (Sharma et al, 1996). It may be available in a depot formulation in the near future.

Gastrointestinal side-effects including nausea, dyspepsia and abdominal pain are reported. There is a significant elevation of prolactin levels and a sedative effect. Although dystonias and akathisias have been reported, risperidone is less likely to produce EPS than classic antipsychotics at the current recommended doses (Kerwin, 1994).

Sertindole

Sertindole was introduced in the UK in 1996. It has a high affinity for D_2 receptors. It selectively blocks D_2 receptors in the mesolimbic cortical bundle with relatively little effect on D_2 receptors in the nigrostriatial pathway and the tuberoinfundibular system. It has high affinity for $5HT_2$ and α_1-adrenergic receptors.

It has fewer EPS, but electrocardiographic (ECG) changes are observed, such as prolonga-

tion of the QT interval. Sertindole is therefore contraindicated in patients with clinically significant cardiac problems. Postural hypotension is another side-effect. When initiating treatment, the starting dose is 4 mg daily which is then increased over 11 days to 12 mg daily in adults. A lower titration dose is recommended for the elderly. No clinically significant changes in prolactin levels are reported. There is no haematotoxicity. Side-effects include decreased ejaculatory volume and nasal congestion.

Ziprasidone

Ziprasidone is currently in phase three clinical trials and is a potent antagonist of D_2 and 5HT receptors. In a 6-week trial of 302 patients with acute exacerbations of schizophrenia, ziprasidone was found to be superior to placebo with respect to both positive and negative symptoms (Reeves, 1996; Tandon et al, 1997). Studies involving active comparators are lacking.

Clozapine

This is a multiple affinity drug. It has weak affinity for D_2 receptors and is more active at D_4 receptors. It has greater antiadrenergic and anticholinergic activity, and high affinity for serotonergic receptors.

Clozapine has fewer EPS than conventional antipsychotics and causes more sedation. It induces postural hypotension, and it has more anticholinergic side-effects in comparison to chlorpromazine. It causes agranulocytosis in 2–3% of patients taking the drug, and its use is therefore restricted to patients registered with the clozaril patient monitoring service, whereby the patient has a regular full blood count to detect any possible agranulocytosis. It also produces hypersalivation and rarely myocarditis.

About 30% of schizophrenics will respond within 8 weeks and a further 30% will do so within 12 months. Studies show that the risk of neutropenia is 1–2% and these patients recover their blood status within 4 weeks (Launer, 1993). Clozapine is found to improve pre-existing tardive dyskinesia and rarely causes it (Taylor, 1995). The severity of EPS appears to be comparable with clozapine and placebo (Pickar et al, 1992).

Olanzapine

Olanzapine was introduced in the UK in 1996. It has moderate affinity for D_2 receptors and preferentially blocks D_2 receptors in the mesolimbic cortical bundle. It has high affinity for $5HT_2$ receptors and muscarinic receptors, and low affinity for α-adrenergic receptors. Olanzapine's actions are more pronounced in limbic than in striatal areas and this makes it less vulnerable to EPS (Tamminga et al, 1997).

It has fewer EPS than traditional antipsychotics, but this benefit may be lost at doses over 10 mg daily. Doses of olanzapine greater than 12.5 mg/day may increase the incidence of EPS above placebo levels (Medicines Resource, 1997). No marked ECG changes are observed. Postural hypotension is not marked and treatment can be initiated at therapeutic doses. There is no associated agranulocytosis. Side-effects include weight gain and somnolence. Early dietary counselling would seem a worthwhile intervention to prevent excess weight gain.

Quetiapine

Quetiapine was introduced in the UK in 1997. It has comparable affinities for D_2 and $5HT_2$ receptors (Meltzer, 1992; Saller and Salama, 1993). It demonstrates limbic selectivity (Chiodo and Bunney, 1983; White and Wang, 1983; Goldstein et al, 1993). Quetiapine shows no sustained effect on serum prolactin levels (Meltzer et al, 1975; Saller and Salama, 1993). It is associated with minimal dystonic liability in haloperidol-sensitized and drug-naïve monkeys (Casey, 1989; Migler et al, 1993). It has weak affinity for D_2 dopamine receptors, high affinity for $5HT_2$ serotonergic receptors and α-adrenergic receptors and no affinity for muscarinic receptors.

Minimal EPS are observed. In placebo-controlled studies, the incidence of acute EPS with quetiapine was found to be not significantly different from placebo (Meats, 1997). The incidence of EPS with quetiapine is not different to placebo even at the top of the recommended dose range (Arvanitis et al, 1997). ECG changes are reported, such as prolongation of QT interval. Postural hypotension is reported. The initiating treatment dose is 25 mg twice daily which is then increased to 150 mg twice daily over 4 days. There is no associated agranulocytosis. Some disturbance in liver function tests (LFTs) is noticed. There is only a negligible increase in prolactin levels. Side-effects include headaches and somnolence.

Zotepine

This atypical drug has been marketed in some countries including Japan and Germany and is in phase three clinical trials in others. Its antipsychotic effect has been confirmed in several open trials and in double-blind comparative European

trials against perazine and haloperidol. Zotepine has shown to be superior to haloperidol in treating negative symptoms in a double blind, randomized comparison in 30 people with schizophrenia of the residual type and having severe negative symptoms (Barnas et al, 1992). Over 1.7 million people have received this drug. Even though its effects on negative schizophrenic symptoms have been well proven, evidence for an effect on primary symptomatology independent of changes in negative symptomatology and EPS has yet to be found (King, 1998).

Amisulpiride

Amisulpiride was introduced in the UK in 1997. It blocks D_3 receptors (mainly presynaptic) and D_2 receptors (mainly postsynaptic at high doses). It is limbic selective, and has low affinity for $5HT_2$ receptors, α-adrenergic and muscarinic receptors.

Amisulpiride has a lower potential for causing EPS, but this benefit is lost at the maximum dose. At lower doses (100–300 mg amisulpiride) shows efficacy on negative symptoms, with more conventional antipsychotic efficacy coming with higher doses (600–1200 mg).

One comparative study has shown amisulpiride to be superior to haloperidol in treating negative symptoms (Moller et al, 1997). ECG changes are not marked and do not require routine ECG monitoring. Postural hypotension is reported but treatment can be initiated at therapeutic doses (200 mg twice daily). There is no haematotoxicity, and no requirement for routine monitoring of LFTs. Some reversible elevation in prolactin levels associated with clinical manifestations have been observed. Side-effects include insomnia, anxiety and agitation. A recent study has indicated that amisulpiride has better efficacy for depressive symptoms than conventional drugs in acute cases (Muller and Benkert, 1998).

DISCUSSION

Even though the classification of schizophrenic symptoms is a matter of controversy, there is general agreement on the definition of positive and negative symptoms. Flattened affect and poverty of speech are accepted unanimously as the core negative symptoms. The four key dimensions of 'atypicality' are thought to be greater efficacy against negative symptoms and mood symptoms, very favourable EPS profile and negligible effect on prolactin. Clozapine is considered as a prototype.

More studies have to be undertaken before arriving at any firm conclusion regarding comparative efficacy and tolerability of the different classes of atypical antipsychotics, as good head-to-head comparison studies are currently rare. It is not advisable to keep patients on anticholinergic drugs which have their own side-effects and tend to antagonize the antipsychotic benefits (World Health Organization, 1990). Atypical agents are warranted when patients may be at risk from prolonged administration of anticholinergic drugs.

Patients are particularly sensitive to EPS, and their mental resources for recovery are greatest in the first episode, so the ideal time to use a novel atypical drug is in the first episode (Lieberman, 1996). Amisulpiride or risperidone should not be given to patients with a history of problematic EPS on conventional drugs. Olanzapine and quetiapine are not advisable for patients with obesity or when over sedation is not desirable.

Patients on conventional antipsychotics also suffer from cumulative side-effects. The past 3 years have seen a major change in the treatment of psychotic patients. The novel atypical antipsychotics have become the first line of treatment for psychoses even though they are more expensive, as they are proven to have distinct and important advantages. The drug-induced movement disorders are more prevalent with older age groups. The newer drugs help provide both better tolerability and fewer disadvantages to the elderly. When depot medications are stopped while newer drugs are being introduced in their place, anticholinergic cover can also be withdrawn; an additional advantage. In general, psychiatrists are reluctant to stop depot medications as these treatments ensure that the patient is receiving the drug, but patients also feel restricted. The newer drugs make them feel more independent, as well as experiencing improvements in side effects.

GPs have proven resistant to change because of the expense of newer drugs over the conventional antipsychotics, and they have to be brought around. The greatest drawback of atypical antipsychotics is their weight-gaining side-effects, which may be a disadvantage in elderly patients with osteoarthritis.

Once atypical drugs become widely used, they graduate as 'typical agents' in clinical practice (Reus, 1997). Patterns of treatment have been ingrained in patients and their carers, and they do not like change. Anything new, however good it may be, is a disturbance to the tranquillity of the mind. The novel neuroleptics are not a panacea. HM

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KEY POINTS

- The newer antipsychotic drugs have greater efficacy against negative symptoms.
- Mood symptoms are improved by the atypical neuroleptics.
- The novel antipsychotic drugs have a favourable extrapyramidal side-effect profile.
- They have a negligible effect on prolactin levels.