Pharmacotherapy of Schizophrenia in Germany

Mathias Bartels

Psychiatrische Universitaetsklinik, Tuebingen, Germany

(Received for publication on October 5, 1991)

Abstract. The practice of pharmacotherapy of schizophrenia in Germany is based both on clinical experience and research findings. Experience and studies emphasize that neuroleptic medication is severely limited by side effects including acute extrapyramidal syndromes and tardive dyskinesia. Comparing neuroleptic doses in both acute and maintenance therapy have clinicians encouraged to evaluate methods for treating patients with the lowest effective dose. Other studies have shown that the plasma level may be helpful when deciding which is the best treatment for the illness. More precise results for determining the optimum dose of antipsychotic compounds in the future may be available from positron emission tomography (PET), and from fluorine-magnetic-resonance spectroscopy (FMRS). The management of patients whose illness are refractory to conventional neuroleptics is also discussed. Benzamides and clozapine, both atypical neuroleptics, may be more effective than other available compounds for the severely ill, or for patients who are unable to tolerate the neurological side effects of typical neuroleptics.


Key words: neuroleptics, postpsychotic depression, clozapine

Introduction

Neuroleptic drugs are effective for both the treatment of acute schizophrenic psychosis and the prevention of relapse in those patients who have recovered from the illness. However, these drugs have a number of important limitations, in most cases caused by their adverse effects. This lecture will first describe the strategies that researchers have chosen for addressing these limitations and then focus on recent change in treatment practice which have resulted from clinical research with special reference to the practice in Germany.

Which Type of Neuroleptic

Although many conventional neuroleptics are currently available in Germany none has been shown to be more effective than the other. However there is a hit-list of the most prescribed drugs in Germany. This information is based on group data and cannot be strictly applied to individual cases. It is possible, for instance, that a patient may respond well to one drug and be unaffected or even worsened by another. Clinical experience has shown that patients past response to various neuroleptics can often guide the selection of a drug. Neuroleptics are not equivalent in their side effects. Generally the high-potency compounds like phenothiazines, butyrophenones and thiothixenes have less sedation, fewer anticholinergic effects, but at a cost of producing more extrapyramidal effects, mainly drug-induced parkinsonism, acute dystonia and akathisia, compared to the low-potency neuroleptics. The choice which drug to use is generally made by considering the side effects though no consensus is available. Many clinicians feel that the side effect profile of the high-potency agents is easier for them to manage and is better tolerated by the patients. This clinical impression may account for the fact that the dose (in chlorpromazine equivalents) of the high-potency agents prescribed is 2–7 higher as the low-potency compound (Baldessarini et al 1988). On the other hand adjunctive medication is frequently more required in giving high-potency neuroleptics, that is to say, anticholinergic, dopaminergic and adrenergic.

Defining the Optimal Dose

Despite massive clinical and research experience with these agents compiled over the last 35 years, the question of the optimal dose is far from being clearly
Plasma Level Measurements for Neuroleptics

Schizophrenics patients differ markedly in the dose of drug that they can tolerate. Some of this variation in the tolerance of the drug is attributable to factors such as individual metabolism, bioavailability, age and weight. Studies from Davis et al. 1989 showed that patients who received the same dose of the drug had large variations in the plasma levels. Therefore measuring plasma levels would provide information that could be useful to clinicians. Unfortunately this enthusiasm was diminished by a number of failures to provide reliable relationships between plasma levels and clinical response. Our new attempt using 19-Fluorine magnetic resonance spectroscopy to measure brain neuroleptic levels would, as we hope, give us more information (Bartels et al., 1986, 1991). Another problem is that each substance has a more or less large number of metabolites, partially active and partially inactive. Therefore a lot of research is needed to find solutions for these problems. Since haloperidol has only a single metabolite, which may not have significant antipsychotic activity. This indicates that measuring plasma from haloperidol concentration may be useful for the clinician. Recently, a well-defined curvilinear relationship between plasma level and dopamine receptor occupancy based on positron emission tomographic studies has been reported by Farde et al and by Wolkin et al. At very low plasma levels of haloperidol, receptor blockade increased rapidly with small increases in the level. The increase in the blockade then tapered off at 5—15 ng/ml; above 20 ng/ml relatively little additional increase in receptor blockade could be measured, even with marked increases in plasma levels. This is in remarkable agreement with clinical experience that there is little added benefit as plasma levels of haloperidol rise above 20 ng/ml (Baldessarini et al., 1988), and a strong argument for the clinical merit of measuring plasma neuroleptic drug level. In Tuebingen we have begun, conducted by Prof. Gaertner with the systematic measuring of the plasma haloperidol levels to optimize the therapy of each patient.

Depressive Symptoms in Schizophrenia and Postpsychotic Depression

It is estimated that between one third and a half of chronic patients have clinically significant depressive symptoms. Depressive symptoms in schizophrenia may occur as a core manifestation of the illness or as the so called postpsychotic depression.6 Rifkin et al and Van Putten & May however, describe the akinetic syndrome as a neuroleptic side effect. Some controlled studies have shown that combining antidepressants with neuroleptics provide no demonstrable advantages over neuroleptics alone. On other hand, it was shown by Prusoff et al., 1979 and Siris et al that depressed schizophrenic patients could be well-treated with adjunctive tricyclic antidepressants. Therapy should be monitored closely because antidepressants may exacerbate psychotic symptoms. In Tuebingen we restrict the dose of antidepressants usually to 75 mg/day. In a recent study of Hippius et al12 it was shown that some side effects of the neuroleptics, especially akathisia is markedly reduced by adjunctive therapy with amitriptylin in low dose, that means 2 × 10 to 25 mg/day.

Treatment of Neuroleptic Unresponsive Schizophrenia

Between 10 and 25 percent of schizophrenic patients receive little benefit from typical neuroleptic drug therapy (Davis et al., 1980). Though there are some strategies to treat this neuroleptic refractory population.

High dose treatment

One strategy is to set treatment-resistant patients on high dose therapy. A number of studies support the use of this regimen eg, Rifkin et al.13 However a study from Quitkin14 blindly compared two extremely different doses of fluphenazine (30 and 1200 mg/day). The results favoured the standard dose above the “megadose” treatment. Nevertheless in individual cases such treatment could be recommended, but side effects of the extrapyramidal system, especially the so called “neuroleptic malignant syndrome” most be carefully observed.
Carbamazepine

In recent years there has been strong evidence that carbamazepine combined with neuroleptics may be beneficial in treating schizophrenia. Adding carbamazepine to neuroleptics may be helpful in patients with history of epilepsy or signs of brain damage. There is to pay attention on the fact that carbamazepine reduces plasma levels of neuroleptics, presumably by induction of hepatic enzymes.

Lithium

Lithium is a very helpful agent in the treatment and prophylaxis of affective diseases. Combined with neuroleptics, it is shown to benefit patients with excited schizo-affected illness (Biedermann, 1979) and schizophréniform illness. Small et al. reported that combining lithium and neuroleptics in chronically hospitalized patients reduced symptomatology. In clinical experience it has been shown that adjunctive Lithium is helpful for patients who have a clear affective component contributing to their illness. On the other hand attention must be drawn to the fact that chronic schizophrenics often have problems with compliance though lithium therapy is usually restricted only to a well-observed population, that is to say, hospitalized patients.

Beta-blockers

Yorkston, Lindstrom, and Pugh reported improvement with the addition of propanolol in a high dose (400 to 2000 mg/day) to a standard neuroleptic regimen. In Germany high dose propanolol adjunctive therapy has been given up. In some cases with high pulse rates caused by anxiety or as a side effect of clozapine we give as adjunctive therapy 3 x 20 to 40 mg propanolol. As propanolol like the antidepressants elevates plasma neuroleptic levels, care should be excercised in monitoring for an increase in side effects.

Benzodiazepines

The literature on the use of benzodiazepines in treatment refractory schizophrenia is divided, most reports have shown a lack of efficacy. However we could shown that some symptoms and some side effects, particularly akathisia was markedly reduced by combining lorazepam with neuroleptics. In our opinion anxious symptoms of schizophrenia and akathisia cannot be clearly seperated, therefore we prefer in such states a combined neuroleptic and benzodiazepine therapy (Bartels et al., 1987)

Long Term Maintenance Strategies

It is well established that treating remitted schizophrenic patients with neuroleptic drugs substantially lowers their rate of relapse. However, longterm maintenance therapy is associated with neurological side effects, the most serious problem being tardive dyskinesia. When drugs cannot be discontinued, the only strategy for reducing the risk of tardive dyskinesia was, before the availability of clozapine to treat patients with the lowest effective dose. With the availability of clozapine our strategy is to try set the patient on this compound when first signs of tardive dyskinesia arise. We published a study, (Bartels, 1988) showing that even in serious cases there is a marked reduction of symptoms. We plan to replicate this results by using zothepine, a new compound from Japan, now introduced also in Germany, the trade name is Nipoleptr, also being free from extrapyramidal side effects. There are other reasons besides tardive dyskinesia for reducing the dosage neuroleptics in maintenance therapy. Extrapyramidal side effects, particularly akathisia and akinesia worsen often the clinical condition of the patient. Akathisia is defined as the feeling of restlessness. In a study from Van Putten et al. it was found that upto 60% of patients treated with a high-potency neuroleptic experienced some form of akathisia within seven days of starting the drug. Akinesia is a state which may be manifest in decreased spontaneous movement, diminished conversation and apathy. These symptoms show resemblance to the flattened affect and decreased motivation that characterize negative symptoms of schizophrenia. It is therefore understandable that they are frequently not well recognized. Concern about the above mentioned side effects lead to a search for methods for treating schizophrenic patients with the lowest effective dose.

Intermittent or target treatment

Its proponents recommend gradually decreasing the amount that stable patients receive until they are completely discontinued. The patients are then observed closely until there are signs that they are beginning to relapse. Then the drugs are reinstiuted. To make the strategy work, patients and their relatives are trained to detect prodromal signs of impending psychotic breakdown in order that drug treatment can resume before the patient becomes floridly ill. A recent report by Jolley, 1989, indicates that patients who were assigned to intermittent treatment were more likely to have recurrence of psychotic symptoms. However, these recurrences were relatively mild and seldom lead to hospitalization.
Reduction of the dose

Kane et al. treated stabilized outpatients with doses of fluphenazine decanoate that were only about one-tenth of the amount usually prescribed. Most patients on this regimen remained remitted for six months. Studies from Marder et al. indicate that when a low dose of fluphenazine decanoate is set at 5 mg every two weeks rates of mild psychotic exacerbation are comparable to a conventional dose of 25 mg during the first year of the study, but significantly higher during the second year. However the clinician should have the flexibility to double the dose when they demonstrate psychotic symptoms. This strategy is not usefull in the case of schizophrenic patients with violent suicidal attempts and anti-social behaviour. This strategy is not useful in the case of schizophrenic patients with violent suicidal attempts and antisocial behaviour. If in this group of patients a serious extrapyramidal effect become apparent we usually give clozapine with very good clinical results.

Clozapine

This drug is pharmacologically different from all of the available neuroleptics. Whereas conventional neuroleptics have strong affinity for the D2 dopamine receptors, clozapine has relatively weak affinity for D1 and D2 receptors. In addition to being a potent anticholergic agent, it has also significant blocking effects for 5HT2, alpha and histamine H1 receptors. The weak dopamine-blocking effect probably explains why clozapine produces only minimal elevation in serum prolactin, and why clozapine causes negligible extrapyramidal side effects. Given these advantages of clozapine, it was hoped that the availability of the drug would represent a major innovation in the treatment of schizophrenia. However widespread use of clozapine in Europe revealed a high rate of agranulocytosis. This lead to a stop or a strong restriction in the clinical application of clozapine. Nevertheless this compound has been clinically available in Germany again since the 1980. Clinicians will be required to adhere an intensive monitoring system, including a weekly red and white blood cell count for the first 18 weeks after starting the drug. Despite risk of agranulocytosis clozapine is an important drug for patients with a schizophrenic illness that is refractory to other compound, the benzamides, including sulpirid, amisulprid and remoxipride become more and more important as an alternative to the classical neuroleptics. Sulpiride has an interesting effect. In low dose up to 300 mg/day there is more an antidepressive effect, in doses between 400 and 1200 mg/day there is a mild but clear antipsychotic efficacy. However there are two disadvantages. First, the onset of neuroleptic effect is delayed by some days (up to 7). This explain by the slow penetration rate of this compound in the brain. The second disadvantage is the marked rise in prolactin, originating from strong dopamine D2 blockade in the tubero-infundibular system. Extrapyramidal effects are extremely rare, though the substance is well tolerated by the patients. The same is the case with remoxipride, with the exception that this compound more rapidly passes blood brain barrier.

References

8. Van Putten T, May PRA: Akinetic depression in schizophrenia. Arch Gen Psychiatry 1978, 35: 1101–1107