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Are Neuroleptics Effective and Specific? A Review of the Evidence

In this chapter I will look at the main body of research on which current beliefs about the nature and efficacy of the so-called antipsychotic or neuroleptic drugs are based. I will attempt to evaluate whether the data from this and other research supports a disease-based theory of neuroleptic drug action in disorders diagnosed as psychosis or schizophrenia.

Are neuroleptics better than placebo for short-term treatment?

There is no doubt that neuroleptic drugs have profound effects on the human body and brain. The question that we need to ask about their short-term use is whether they have any clinical advantage over placebo, *and* over other sorts of drugs that might be used in people with acute psychosis. By advantage we could mean a number of things. Firstly we could ask whether antipsychotic drugs speed up the natural process of recovery from psychosis, that is, do people get better quicker than they would without them? We know, for example, that for most people periods of psychosis are self-limiting. Secondly we could ask whether people who were prescribed these drugs achieve a fuller recovery when compared with people taking no treatment, placebo or other types of drug. Finally we might want to know whether these drugs help more people to recover than would do otherwise. One immediate problem with addressing these questions is that our information about the natural history of acute psychosis without modern drug treatment is limited. We do not actually know how many people might get better without drug treatment, how fast or how completely.

Studies of the effects of short-term treatment show that being on a neuroleptic is superior to being on an inert placebo on measures of

symptoms and behaviour over a relatively short period. Since many episodes of acute psychosis are likely to last for months at least, and all such trials last a few weeks at most, there is little data with which to consider the overall advantages of drug treatment on the outcome of an acute episode. However these studies demonstrate that patients taking placebo also improve and in some trials the difference between the drugs and placebo is not large (Johnstone et al. 1978).

Longer-term follow-up of the results of acute treatment studies are rare. A one-year follow-up study of the earliest trial conducted by the NIMH in the United States found no evidence that patients who had been randomised to drug treatment fared better than those randomised to placebo. In fact the placebo group had a lower rate of hospital readmission during the year of follow-up, which was the only statistical difference between the two groups (Schooler et al. 1967). Similarly follow-up of another randomised trial with patients with first episode psychosis found that only 27% of the placebo group were rehospitalised compared with 62% of the patients initially randomised to chlorpromazine ($\chi^2=8.43$, $p<.01$) (Rappaport et al. 1978). The three-to-five-year follow-up of a large randomised trial comparing neuroleptics with psychotherapy, milieu therapy (consisting of admission to a well staffed hospital ward with no specific additional treatments) and ECT showed little difference between the groups. This was despite the fact that the short-term results showed clear differences in favour of drug treatment. The follow-up results were especially remarkable since the study excluded 'good prognosis' patients who were expected to do well without drugs (May et al. 1981). Between 15% and 44% of patients who were not allocated to antipsychotic drug treatment during the initial study phase managed to avoid the use of neuroleptic drugs for at least three years of follow-up. Therefore research suggests that neuroleptic drugs reduce the symptoms of psychosis or schizophrenia over the short term in some patients compared with the use of placebo, but there is little to suggest that this has any ultimate benefit.

The concept of 'treatment-resistant schizophrenia', which was developed to delineate a market for the relaunch of clozapine, has led to public acknowledgment of the extent of non-response to treatment with other neuroleptic drugs. It is now widely admitted that at least 25% of patients do not show any significant clinical improvement with drug treatment. A recent comparison of two of the newer neuroleptic drugs, risperidone and olanzapine, found that 46% and 56% of patients, respectively, did not respond after four months of treatment (Robinson et al. 2006). In addition, the majority of inpatients with psychosis are treated with other sedative drugs in addition to

neuroleptics, implying that the neuroleptics alone are insufficient to control their symptoms. In 1995, a survey found that 70% of patients on neuroleptics were taking other psychotropic medications, mostly benzodiazepines and “mood stabilisers” (Baldessarini, Kando, & Centorrino 1995). Therefore, it seems that antipsychotics are often unable to significantly improve the condition of someone who is acutely psychotic.

Are neuroleptics better than other drugs for short-term treatment?

The next important question is whether the short-term improvement produced by neuroleptics is better than that obtained with other sorts of drugs. Table 6.1 shows that studies have found that a variety of drugs have comparable effects to neuroleptics in the treatment of psychosis or schizophrenia. Two early randomised trials concluded that barbiturates were inferior to neuroleptics, but these may have been influenced by negative expectations of barbiturates, which were part of the old generation of disregarded drugs and are referred to in the studies as the ‘control medication’ (Casey et al. 1960, p. 98).

After the introduction of the benzodiazepine drugs in the 1960s, several studies were conducted evaluating their effects in schizophrenia. Since benzodiazepines were fairly new at the time, they did not suffer from the

Table 6.1 Studies comparing neuroleptics to other sedatives for short-term treatment of psychosis or schizophrenia

Drug group	Studies	Results
Barbiturates	2 randomised controlled trials (Casey et al. 1960a, 1960b)	Barbiturates inferior to chlorpromazine
Opiates	1 randomised controlled trial (Abse, Dahlstrom, & Tolley 1960)	Opium equivalent to chlorpromazine
Benzodiazepines	6 randomised controlled trials (Hankoff, Rudorfer, & Paley 1962; Hekimian & Friedhoff 1967; Maculans 1964; Merlis, Turner, & Krumholz 1962; Nishikawa et al. 1982; Smith 1961)	Benzodiazepines equivalent to neuroleptic in three studies, superior in two, inferior in one
Lithium	2 randomised controlled trials (Braden et al. 1982; Johnstone et al. 1988)	Lithium equivalent for moderately ill patients; inferior for overactive patients

same stigma as the barbiturates. Ratings of their effects might therefore be less susceptible to bias. Wolkowitz and Pickar (1991) reviewed 14 double-blind trials comparing benzodiazepines with placebo and neuroleptics for the treatment of psychosis or schizophrenia. The studies suffered from problems such as small sample sizes, short duration and mixed groups of chronic and acute patients. Six studies compared a benzodiazepine and placebo for patients with acute and chronic psychotic disorders; only the largest study found the benzodiazepine to be markedly superior to placebo at a statistically significant level. However in the six trials comparing benzodiazepines with neuroleptics, the outcomes were equivalent in three, the benzodiazepine was superior in two, chlorpromazine was superior in one, and in one trial the benzodiazepine was equivalent to haloperidol but inferior to chlorpromazine. Most interestingly, in seven of the ten studies where psychotic symptoms were evaluated, benzodiazepines reduced symptoms as much as neuroleptics or better than placebo. A recent study of the treatment of early signs of exacerbation in schizophrenia found that diazepam was superior to a neuroleptic (Carpenter, Jr. et al. 1999).

Trials of lithium in patients with acute psychosis (and not just mania) showed that lithium was inferior for the treatment of severely overactive patients, presumably because of its toxicity, but comparable to neuroleptics for the treatment of less overactive patients, regardless of diagnosis (Braden et al. 1982; Johnstone et al. 1988). A trial conducted in the 1960 comparing opium and chlorpromazine in acute schizophrenic patients showed equivalent improvement over three weeks with both drugs (Abse, Dahlstrom, & Tolley 1960).

The drug-centred model of drug action suggests that neuroleptics might be superior to other sedative drugs because of the nature of the neurological state they induce with its characteristic psychic indifference. Overall however there does not appear to be strong evidence that the effects of neuroleptic drugs are superior to the effects of other drugs with sedative effects, except possibly the barbiturates. There is little evidence even that they are superior for the core symptoms of psychosis such as delusions and hallucinations, since most comparative studies found benzodiazepines to have equal effects on these symptoms.

Are neuroleptics better than placebo for long-term treatment?

There is overwhelming consensus in psychiatric circles that continuous use of neuroleptic drugs by people with episodes of psychosis or schizophrenia reduces the risk of relapse or deterioration considerably.

Common estimates are that 80% of people relapse without drug treatment compared with 20–40% with drug treatment (Hogarty & Ulrich 1998). Guidelines recommend that people should remain on drug treatment for one to two years after an episode or relapse (National Institute for Clinical Excellence 2002), but in practice professionals are extremely reluctant to stop medication and people are likely to remain on drugs indefinitely unless they actively challenge medical advice and decide to stop the drugs themselves. A recent study found that people with long-term schizophrenia under the care of a General Practitioner had not had their psychotropic medication changed to any degree for decades in some cases, despite being clinically stable for long periods (Challoner 2006).

However the studies of maintenance therapy on which current recommendations are based are deeply flawed and cannot yield data on the efficacy of preventing relapse. This is due to the confounding effects of discontinuation-related problems. These studies start by selecting a group of people who are already taking drug treatment, and whose mental condition is currently stable. These people are then randomised either to continue drug treatment or to have the drug withdrawn and replaced by inert placebo tablets or injections. The placebo group are, therefore, vulnerable to all the adverse effects of having their drug treatment discontinued. The fact that it is usually done quite rapidly is likely to exaggerate these effects. Therefore, the fact that outcomes of patients allocated to placebo in long-term discontinuation trials appear to be inferior to those of people who stay on medication may merely reflect the difficulties of stopping long-term drug treatment. Somatic withdrawal symptoms may be mistaken for signs of relapse. The pharmacological stress placed on the body by withdrawal may induce a relapse and a small proportion of people may experience an episode of psychosis that is part of the withdrawal syndrome and may be nothing to do with their original condition (Moncrieff 2006). In addition, there are the likely effects of negative attitudes of staff, patients and others towards being on placebo. Most people who work in the mental health system believe that drug treatment is beneficial and that withdrawing it will inevitably lead to the recrudescence of the underlying problem. Given that people taking neuroleptics and placebo are likely to be easily distinguished on the basis of the many obvious effects of neuroleptics, such as extrapyramidal effects, it is possible that negative expectations further depress the outcome in the group withdrawn to placebo. Staff might overreact to minor withdrawal symptoms, for example, or focus on negative events that would normally be ignored in people they suspect have been withdrawn from drugs. One study revealed nursing staff's negative attitudes to reducing medication and concluded that

staff attitudes were just as important as a patient's mental condition in determining drug treatment (Thomas, Katsabouris, & Bouras 1997).

A large review of 66 discontinuation studies published in 1995 found that overall, over an average period of 10 months follow-up, 16% of patients who continued drug treatment relapsed compared with 53% of patients who discontinued drug treatment (Gilbert et al. 1995). Further analysis of this set of studies revealed that the relapses after medication discontinuation were clustered around the point at which the drugs were stopped. Fifty per cent of those relapsing did so within three months of discontinuation (Baldessarini & Viguera 1995). In studies using randomised or matched controls, the risks of relapse after discontinuing medication appeared to converge over time with the risk of relapse while staying on medication. In other words, with increasing time after drug withdrawal the increased risk of relapse seemed to dissipate. Another meta-analysis of 28 discontinuation studies, mostly randomised controlled trials, confirmed these findings (Viguera et al. 1997). After abrupt discontinuation of drug treatment relapse risk was 50% within 30 weeks and by six months following drug discontinuation there were few further relapses. Overall 54% of patients relapsed in the first year after discontinuation compared with a further 2% in the following year.

There are at least two explanations for the clustering of relapses around drug withdrawal. The first is that somatic discontinuation symptoms are mistakenly labelled as relapse. The second is that the withdrawal process itself provokes significant psychopathology, either in the form of a withdrawal-related psychotic episode, or in the form of withdrawal-induced relapse of the underlying condition. Several studies included in Gilbert et al.'s review used broad criteria for relapse, such as small increases in rating scale scores that may easily have led to misdiagnosis of people experiencing somatic discontinuation symptoms. In addition, in many early studies relapse was not defined at all, but left to the discretion of the treating physician or investigator. In others it was simply defined as the 'need to resume treatment'.

If mild discontinuation symptoms can be mistaken for relapse, it would be predicted that studies that used hospitalisation as the relapse criterion would find smaller differences between drug treatment and placebo than other studies. The only study included in the Gilbert et al. (1995) meta-analysis to define relapse exclusively as hospitalisation found a difference of only 17% in relapse rates between people who continued to receive drugs and those withdrawn to placebo after two years (Carpenter, Jr. et al. 1990). This compares with an average difference in relapse rates of 37% at 10 months for all studies included in the analysis.

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So there is an indication that some of the excess morbidity in the placebo group in randomised maintenance trials represents mild somatic withdrawal symptoms, or psychological symptoms relating to withdrawal, which are mistaken for signs of impending relapse. It is difficult to judge what proportion of severe relapses represent the re-emergence of the underlying illness in the absence of treatment, and what proportion may be episodes provoked by medication withdrawal. Studies among people with first episode psychosis may be instructive, since they are likely to have a shorter exposure to drug treatment than people with a long history of psychiatric disorder. This does not eliminate the possibility of drug withdrawal-induced psychosis and relapse since patients are likely to have been taking medication for some months at least, but it may mean these phenomena are less common. Mistaking withdrawal symptoms for relapse is still a potential problem.

Surprisingly there is only one placebo controlled trial conducted with people experiencing their first episode of psychosis. It took place at Northwick Park hospital in London and was published in 1986 (see Figure 6.1) (Crow et al. 1986). Relapse was defined as readmission to hospital or need for resumption of antipsychotic treatment. Follow-up

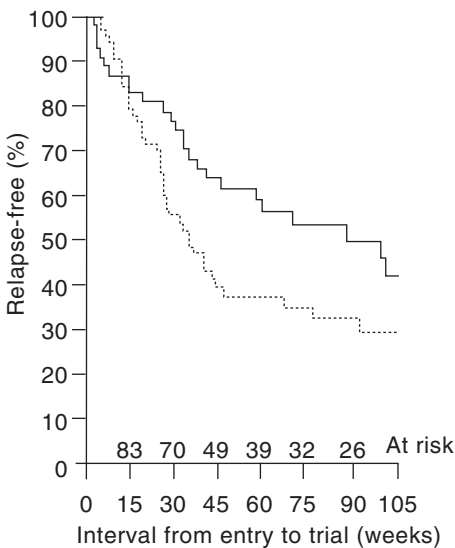


Figure 6.1 Northwick Park first episode study: Percentage of patients remaining relapse free on drug and placebo (reproduced with kind permission of the Royal College of Psychiatrists)

lasted two years. The results show a possible discontinuation effect, with the majority of placebo group patients relapsing in the first year and relatively few thereafter. In contrast, the drug-maintained patients continue to relapse throughout the second year.

Overall 46% of 54 patients on active medication were diagnosed as relapsed compared with 62% of 66 patients on placebo, giving a difference of 16%. Most patients defined as 'relapsed' were said to have psychotic symptoms, but not all. Since no breakdown is given by treatment group, it is difficult to judge whether some relapses on placebo might have been unrecognised drug-withdrawal symptoms.

Relapse rates in a more recent comparative study of haloperidol and risperidone for first episode psychosis were similar (Schooler et al. 2005). Forty-two per cent of the risperidone group and 55% of the haloperidol group were diagnosed as relapsed during the follow-up period of up to five years. However since rates of discontinuation were high (37% in the haloperidol group, 42% in the risperidone group), the proportion of patients who stayed in the study and had not relapsed at two years was only 28% of the haloperidol group and 44% of the risperidone group. Thirty-eight per cent of patients on placebo in the Northwick Park Study had not relapsed at the end of the two-year follow-up. Another large, government-funded trial, referred to as the CATIE study (Clinical Antipsychotic Trial of Intervention Effectiveness) consisted of a comparison of treatment with different neuroleptics in naturalistic conditions in people who were mostly stable and not treatment resistant. This study found that the median duration of 'successful' treatment¹ was only three months with olanzapine and one month with the other drugs (Lieberman et al. 2005a)!

Studies of long-term drug treatment in schizophrenia and psychosis emphasise relapse at the expense of other aspects of outcome such as social or occupational functioning or subjective effects. This is partly because relapse is considered to be an indisputable catastrophe, which trumps all other considerations. This helps to reinforce the disease-centred model, obscuring the impact of the global effects that drugs produce. The fact that almost all RCTs of maintenance treatment stop at the point of relapse confirms this way of seeing things, by generating a limited set of data. If patients were followed through relapses, firstly it would allow for discontinuation effects to dissipate and secondly it would enable a comparison of outcome in a number of different realms over a period of time.

Discontinuation effects also mean that in ordinary clinical practice people who take long-term medication and stop or reduce it for any

reason (especially if this is done abruptly) may be more likely to relapse than they would be if they had never started on long-term treatment. In other words, long-term treatment may produce the very problems for which it is prescribed.

Neuroleptic drugs and long-term outcome of schizophrenia

Since the 1950s extravagant claims have been made about the impact of neuroleptic drugs on the outcome of schizophrenia. Modern textbooks of psychiatry still assert that the drugs were responsible for the decline in mental hospital populations, despite contrary evidence (Cookson 2005, p. 9). The authors of a meta-analysis of outcome studies over the 20th century, attribute the apparent improvement of outcome between the 1950s and 1980s to the introduction of the new drug treatment, among other things. However in the 1990s improvement rates declined to levels comparable with those found in the early part of the 20th century prior to the availability of modern drugs. Hence, the review provides no strong evidence that drug treatment has improved outcome (Hegarty et al. 1994).

Comparing outcome studies conducted at different times in this way is complicated by variations in diagnostic fashions and judgements of outcome. What is considered a good outcome in one era may not be considered so in another historical context. Similarly diagnostic fashions are known to have varied considerably over the 20th century. A study that retrospectively compared the outcome of patients admitted to psychiatric hospitals in 1947, just before the introduction of neuroleptic drugs with those admitted just after their introduction, in 1957, is useful in this respect (Bockoven & Solomon 1975). There was little difference in outcome between the two cohorts with 76% of the earlier cohort living in the community at five-year follow-up compared with 87% of the later cohort, despite the political impetus towards community care over the period. The authors of the study concluded that 'these drugs might not be indispensable' (p. 796).

A recent study of people admitted to hospital with a first episode of schizophrenia found that there were an average of two readmissions per person over an average of 3.6 years follow-up (Tiihonen et al. 2006). Another recent five-year follow-up of people with a first episode found that only 14% were deemed to fully recover (Robinson et al. 2004). Figures like these make it difficult to believe that the availability of neuroleptic drugs has much ameliorated the harsh and recurrent nature of this condition.

Not only is it difficult to prove that the long-term and widespread use of neuroleptic drugs has improved the outcome of schizophrenia but there are some hints that it may actually depress the outcome – that drug treatment may make people worse in the long term. It is well known that the outcome of schizophrenia, diagnosed by exactly the same criteria, is worse in the West than it is in the developing world (Jablensky et al. 1992; Leff et al. 1992). This is usually explained as demonstrating the detrimental effects of industrialised society, which is probably partly the case. However Robert Whitaker suggests that these studies provide evidence that drug treatment makes outcomes worse, since use of drugs is lower in the developing world (Whitaker 2002). In addition, as described earlier, follow-up studies of short-term treatment trials have either shown no difference between people initially randomised to placebo or non-drug treatment (May et al. 1981) or a better outcome in the placebo group (Rappaport et al. 1978; Schooler et al. 1967). In the Northwick Park maintenance study a subgroup of patients with good prognostic indicators had a better occupational outcome on placebo than on drugs (Johnstone et al. 1990). A recent follow-up study also found that people who took neuroleptic drugs for a shorter period had better social and vocational outcomes. However this association disappeared in the multiple regression analysis, suggesting it was attributable to other factors that predict outcome (Robinson et al. 2004). In addition, a number of studies have shown that a substantial proportion of people who experience a psychotic episode can recover without the use of neuroleptic drugs. These include the Soteria Project, set up in the United States by psychiatrist Loren Moshier, with the aim of reducing reliance on neuroleptic drugs. Published data showed that around 30% of patients allocated to the project had good outcomes without drugs (Bola & Moshier 2003). More recently a well-conducted study in Finland managed to treat 43% of patients with a first episode of psychosis successfully without neuroleptic drugs (Lehtinen et al. 2000).

Within cohorts of patients in Western settings, patients who consistently avoid the use of neuroleptic drugs do better than those who use them (Bola & Moshier 2003; Carone, Harrow, & Westermeyer 1991; Harrow et al. 2005; Lehtinen et al. 2000). In one long-term follow-up 40% of those people not taking any medication were classified as recovered after 15 years compared with only 5–17% of those who were taking neuroleptic drugs (Harrow et al. 2005). Use of neuroleptics was associated with a highly statistically significantly worse global adjustment and outcome ($p < .001$). In contrast, a recent follow-up study found higher readmission rates and mortality among people not taking

neuroleptic drugs compared to those who were (Tiihonen et al. 2006). However in this analysis people classified as not taking neuroleptics included people who had just stopped them. Such people may be at risk of withdrawal-related problems, which may also include a heightened risk of suicide. Baldessarini and colleagues found a markedly increased risk of suicide after lithium discontinuation, for example (Baldessarini, Tondo, & Hennen 1999).

The association between the use of drugs and poorer outcome is partly attributable to the fact that people with more severe conditions are more likely to be prescribed long-term drug treatment. Or to put it another way, in the Western world, only those with the mildest of disorders who can function at a fairly high level are going to have a chance of evading the ubiquitous prescription pad. However no one has demonstrated that this is the entire explanation. Until then, the possibility that antipsychotic drugs are damaging to the long-term prospects of recovery has to be entertained. Morbidity associated with discontinuing the drugs and drug-induced neurological impairment, described further in the next chapter, provide possible mechanisms for this scenario.

Are the newer drugs better?

A meta-analysis of placebo-controlled studies of atypical or second-generation neuroleptics found only modest differences between the drugs and placebo. The difference in response rates was only 16% and even the authors comment that this seems small (Leucht et al. 2007). However even this figure may be exaggerated due to the many methodological failings of these trials. Most will have been confounded by discontinuation effects, since none of the studies involved only people with a first episode who had not previously been on drugs. Many studies were conducted with people who were previously stable, and then randomised them to have the new drug or placebo. All patients who had previously been on drug treatment and were put on placebo would therefore be susceptible to discontinuation effects. There was also no examination of the integrity of the double blind and it is likely that side effects lead to unblinding in many cases. Dropout rates were high, at 47% overall. The meta-analysis also demonstrates publication bias, with the funnel plot² showing clear evidence of the non-publication of more negative studies. The fact that known side effects of some of these drugs such as extrapyramidal effects and sedation were not detected also suggests that the trials were not reliable. They were all carried out by drug companies for purposes of getting the study drug licensed.

Drug company-sponsored studies suggest that the second generation of neuroleptic drugs are superior to older ones in terms of inducing lower levels of adverse effects, especially extrapyramidal effects and some claim to demonstrate better efficacy (Haro et al. 2005). This is not surprising in view of findings that most comparative studies find the sponsors' drug to be superior (Heres et al. 2006; Kelly, Jr. et al. 2006). Several meta-analyses of studies comparing old and new neuroleptics have now been conducted and they give conflicting results. Some suggest that the newer neuroleptics have a superior profile (Davis, Chen, & Glick 2003) and some show no difference between the new and the old drugs (Davis, Chen, & Glick 2003; Geddes et al. 2000). Government-funded studies have not found the new drugs to be superior. Three of these have now been conducted. A study of veteran patients in the United States using flexible doses of haloperidol combined with an anticholinergic drug to reduce extrapyramidal symptoms found no difference in efficacy between that and olanzapine and no difference in the incidence of extrapyramidal side effects (Rosenheck et al. 2003). Akathisia (unpleasant restlessness) was lower in the olanzapine group, but weight gain was higher. In the CATIE study, sponsored by the NIMH, there were no statistically significant differences in the main outcome between newer drugs versus an older drug, perphenazine, in this case. The main outcome was the proportion of patients who discontinued treatment, not the symptomatic or functional state of the patient. This is a curious outcome for an effectiveness study since it assumes that remaining on drug treatment is beneficial, but the benefits of drug treatment are precisely what the trial was designed to determine. The study found that a slightly higher proportion of patients stayed on olanzapine, although this was not statistically different from the proportions taking the other drugs. People taking olanzapine gained an average of 1 kg per month (Lieberman et al. 2005a). A United Kingdom-based study compared patients randomised to be prescribed a second-generation neuroleptic of the clinician's choice with an older drug of choice (Jones et al. 2006). There were no statistical differences between the groups in terms of symptoms, levels of functioning, quality of life, extrapyramidal side effects, akathisia, compliance and depression. If anything the differences slightly favoured patients randomised to the older drugs. The most commonly prescribed older drug was sulpiride, which is thought to have a relatively high threshold for inducing extrapyramidal effects and the most commonly prescribed second-generation drug was olanzapine. However the authors did not believe that their findings were attributable merely to the frequent prescription of sulpiride, and anyway they note the pharmacological heterogeneity of both groups of drugs.

Evidence for early intervention and preventive drug treatment

Initiatives for 'early intervention' in psychosis are founded upon the observation that people who have a longer evolution of symptoms before they come to psychiatric attention have a poorer outcome in the long term. This observation used to be interpreted as showing that a more severe and globally disabling form of schizophrenia was characterised by a gradual onset of symptoms, whereas an acute onset indicated a less-severe condition. For example, it is generally accepted that people who have a psychotic episode in response to environmental stress generally have a better prognosis. However possibly under the influence of the pharmaceutical industry, which has sponsored much of the research and discussion in this area, the interpretation of the situation has changed. It is now claimed that a longer evolution of symptoms is associated with poorer outcome because of the delay in the patient receiving treatment. A whole new term has been introduced, 'the duration of untreated psychosis' and the notion of the speed of onset as an indication of the inherent severity of the condition has been forgotten. A recent review of evidence concerning 'duration of untreated psychosis' does not even mention this previously common view (Marshall et al. 2005). The only trial published so far, which compared outcomes for patients in areas with Early Detection teams compared with areas without, found that there was no difference between the areas for severity of positive and general symptoms of schizophrenia, global functioning, quality of life, time to remission and the course of the psychosis. Only negative symptoms were better in patients in early intervention areas, but these symptoms are likely to be influenced more by a general increase in professional support than by a specific effect of earlier drug treatment (Larsen et al. 2006). Further research is clearly needed before any benefits of early treatment can be claimed. Despite this Early Intervention teams have already been established in the United Kingdom and other Western countries.

The idea that the occurrence of a psychotic episode can be prevented by treating individuals believed to be at high risk for developing psychosis is also currently fashionable. Two randomised drug trials have been conducted with young people, mostly those referred to child and adolescent services. Those judged to be at 'high risk' for developing psychosis by virtue of having a family history of psychosis or some vague transitory psychotic symptoms were entered into the studies. One study compared olanzapine with placebo (McGlashan et al. 2006) and the other compared a combination of risperidone and cognitive behaviour therapy with usual

care (McGorry et al. 2002). Both studies found that the drug-treated group had lower rates of onset of acute psychosis during treatment. However the olanzapine study did not find a statistically significant difference, and in the risperidone study it was impossible to say whether it was the drug or other aspects of experimental treatment such as cognitive behaviour therapy that made the difference. In the risperidone study the evaluations were also not conducted double-blind. About a third of the non-drug-treated groups developed psychosis in both studies, but only 12% were classified as having schizophrenia in the one study that gave a diagnostic breakdown (McGorry et al. 2002). In the olanzapine study drug-treated participants gained 9 kg of weight during a year.

Preventive treatment has been criticised on ethical grounds because, even if it works, it involves treating people who will never develop psychosis in order to prevent some cases. The notion of the high-risk individual is also worryingly vague and could easily be expanded to include the majority of young people who attend psychiatric services. Combined with the popularity of the notion of early intervention, the idea of preventive treatment seems likely to decrease the prescribing threshold in child and adolescent services. Evidence suggests that this is exactly what is happening, with prescriptions of antipsychotics to this age group rising rapidly over recent years (Olfson et al. 2006). This should be a major cause of concern, given the vulnerability of the developing brain and evidence presented in the next chapter about the damage neuroleptic drugs can inflict.

The dopamine hypothesis of schizophrenia and psychosis

The dopamine hypothesis of schizophrenia and psychosis appears to justify a disease-centred view of the actions of neuroleptic drugs. However in a tautological loop, it was the action of neuroleptic drugs that gave rise to the dopamine theory in the first place, on the assumption that the drugs act on the biological basis of the condition. In turn the theory has come to be viewed as evidence that the drugs act in a disease-specific way. The action of neuroleptic drugs is still regarded as the strongest evidence for the dopamine theory of schizophrenia. However if their action is understood according to a drug-centred model, as inducing a characteristic neurological state, then it does not follow, as the theory assumes, that psychotic symptoms or the condition of schizophrenia are produced by the opposite biochemical state to that produced by drugs. As we shall see in the next chapter, neuroleptic

drugs dampen down all spontaneous thought and action and their effects are not restricted to psychotic phenomena. Therefore, if we abandon the assumption that neuroleptic drugs act in a disease-centred manner, their effects provide no support for the dopamine theory of schizophrenia.

The other piece of evidence commonly said to have inspired the dopamine hypothesis is that chronic ingestion of stimulant drugs such as amphetamine, cocaine and L-dopa can produce psychotic symptoms in some individuals without a psychiatric history. These drugs increase dopamine activity and it has, therefore, been assumed that this is the mechanism responsible for inducing psychosis. However stimulants affect numerous other neurotransmitter systems. Amphetamine causes a substantial increase in noradrenalin release, for example. Extensive research in the 1970s did not demonstrate what particular aspect of their biochemical activity is responsible for psychosis (Meltzer 1976) and nor did it suggest whether any single neurotransmitter system could be pinpointed, given their complex effects. Dopamine may be involved but so may noradrenalin, other neurotransmitter systems or it may be due to complex interactions between different systems. Or the explanation may lie at another level, like the consequences of prolonged or extreme arousal. Cannabis, which is also well known to cause a psychotic syndrome on prolonged use, does not elevate dopamine levels substantially.

In addition, it has long been recognised that the features of stimulant-induced psychosis are not equivalent to those of schizophrenia (Snyder 1972). Characteristic schizophrenic symptoms such as 'thought disorder' (confused and rambling speech), delusions of control, delusional perception and an inappropriate or flattened mood are rarely seen in stimulant psychoses. In contrast, in amphetamine psychosis mood is usually one of extreme anxiety, sexual behaviour is heightened and visual hallucinations are more common than they are in acute schizophrenic psychosis (Snyder 1972). There is usually also increased motor activity, including sometimes repetitive meaningless, compulsive movements called stereotypies which are not characteristic of schizophrenia or idiopathic psychosis (Batki & Harris 2004). Dopamine is thought to be the main neurotransmitter involved in stimulant-induced hyperactivity and stereotypies, based on animal research that showed that stimulant-induced stereotypies are suppressed by dopamine-blocking drugs to a greater extent than other sorts of drugs (Pycock, Tarsy, & Marsden 1975). It has simply been assumed that because dopamine is involved in causing stimulant-induced

hyperactivity and stereotypy, it must also be the cause of stimulant-induced psychosis. However there is actually no evidence to support this supposition. In addition, some research suggests that noradrenalin may also have a role in increasing locomotor activity (Borison & Diamond 1978; Herman 1970). However since hyperactivity and stereotypies are very uncommon in people with untreated psychosis or schizophrenia, whatever causes them has no obvious relevance for the aetiology of these psychiatric disorders.

It has not been possible to show abnormalities in overall dopamine content of brains of people with schizophrenia. Total dopamine content can, incidentally, only be measured at post-mortem (Scott 2006), and overall such studies have not shown any differences between people with schizophrenia and those without (Reynolds & Czudek 1988). As one of the main researchers in the field put it, 'the dopamine content is found to be normal in the schizophrenic brain' (Seeman 1995). Research into levels of dopamine metabolites in the cerebrospinal fluid,³ which initially claimed to find increased levels in people with schizophrenia, also proved to be inconclusive when people who had not been treated with drugs were investigated (Reynolds 1989; Tuckwell & Koziol 1993).

Findings of increased D₂-receptor density in the brains of people diagnosed with schizophrenia were first reported from post-mortem studies in the 1970s. At first these findings were regarded as evidence of a pre-existing dopamine abnormality in the brains of people with schizophrenia, 'we have now obtained direct evidence for some abnormalities for brain dopamine receptors in schizophrenia' (Lee et al. 1978). However the patients whose brains were examined had been taking antipsychotic drugs for long periods before they died. No one asked the obvious question of whether the observed effects were due to drug treatment, even though it had already been established that antipsychotic drugs increase brain concentrations of D₂ receptors in animal studies (Muller & Seeman 1977). Subsequent post-mortem studies found that the abnormalities of dopamine receptors were entirely attributable to the effects of drugs (Kornhuber et al. 1989; Mackay et al. 1982; Reynolds et al. 1981). In the 1980s it became possible to visualise dopamine receptors in the living brain, using positron emission tomography (PET). One early study of this kind claimed to find increased density of D₂ receptors in brains of 'neuroleptic naïve' patients with schizophrenia (Wong et al. 1986), but these findings were not confirmed in many subsequent studies (Farde et al. 1987; 1990; Nordstrom et al. 1995; Pilowsky et al. 1994). Studies of D₁ receptors

have found them to be unchanged (Cross, Crow, & Owen 1981), decreased (Hess et al. 1987) or more recently increased (Abi-Dargham et al. 2002), although effects of previous drug treatment and age were not fully controlled for in the most recent report. Therefore research has not shown any consistent abnormalities in dopamine receptors in schizophrenia per se. It has demonstrated that neuroleptic drugs, which block the effects of dopamine at D_2 receptors, cause a compensatory increase in the number and density of these receptors in the brain. This finding has been confirmed for some of the new 'atypical' antipsychotics as well as older drugs in recent brain imaging studies (Silvestri et al. 2000).

Despite these findings, some literature still maintains that schizophrenia or psychosis is associated with dopamine receptor abnormalities. A meta-analysis of post-mortem and imaging studies of dopamine receptors failed to mention the confounding effects of drugs, even though the analysis revealed a substantial and statistically significant correlation between the medication status of subjects and D_2 -receptor density compared with controls across studies ($r=0.63$, $p<.05$) (Zakzanis & Hansen 1998).

By the 1990s the lack of evidence of dopamine abnormality combined with data which were obviously contradictory, reduced the popularity and credibility of the dopamine hypothesis of schizophrenia. The existence of negative symptoms seemed incompatible with the idea that schizophrenia is caused by increased dopamine activity, although, as described in Chapter 5, attempts were made to reconcile the dopamine theory with this problem (Davis et al. 1991). The reintroduction of clozapine was also problematic since it appeared to have relatively weak action at D_2 receptors. In order to make its actions consistent with the dopamine hypothesis of schizophrenia, Clozapine is now suggested to have a strong but transient effect on dopamine receptors. However the fact that it does not cause Parkinsonian symptoms at moderate doses suggest that at most it must be a much weaker dopamine blocker than other neuroleptic drugs. Since it is generally considered to be more, not less, effective at reducing psychotic symptoms than other neuroleptic drugs, its action contradicts the dopamine hypothesis.

Since the mid-1990s a diverse and confusing collection of studies have been published which are now regarded as providing evidence that dopamine function is abnormal in acute psychosis. These studies have examined a variety of indirect measures of dopamine activity. Some have investigated the level of increase of dopamine after amphetamine

ingestion (Abi-Dargham et al. 1998; Breier et al. 1997; Laruelle et al. 1996). These studies suggest that, as a group, people with psychosis have an enhanced release of dopamine compared with healthy controls, although there is substantial overlap in results – that is not all patients with psychosis had higher levels of dopamine release than controls. Most studies also showed a corresponding increase in psychotic symptoms in patients after amphetamine ingestion, a phenomenon that has been observed before. This suggests that people with psychosis respond more intensely to stimulant drugs than controls, but this may be a function of their psychological state. In other words, people with psychosis may respond more strongly because they are already aroused. It does not necessarily provide evidence of a pre-existing biological difference.

Another group of studies have measured the uptake of a radiolabelled dopamine precursor molecule, presumed to reflect the synthesis of dopamine in people with psychosis compared with healthy controls (Dao-Castellana et al. 1997; Elkashef et al. 2000; Hietala et al. 1995; Lindstrom et al. 1999; Reith et al. 1994). Results of these are inconsistent. Even the results of the 'positive' studies are incongruous with some finding increased uptake in the putamen but not the caudate nucleus (parts of the basal ganglia) (Hietala et al. 1995) and another finding increased uptake in the caudate but not the putamen (Reith et al. 1994). One study found no effect (Dao-Castellana et al. 1997) and the largest study so far found the opposite finding of reduced uptake in the ventral striatal area of the brain (Elkashef et al. 2000). Two studies examined indirect measures of dopamine-receptor occupancy. Although the authors of one concluded that their results showed 'direct evidence of increased stimulation of D₂ receptors by dopamine in schizophrenia' (Abi-Dargham et al. 2000, p. 8104), effects of prior drug treatment were evident from the results and were not completely controlled for.

All recent studies were small, and although efforts were made to identify and include patients who had not previously taken neuroleptic drugs, known as 'drug naïve' patients, all but one of the studies also included patients who had taken these drugs in the past, often for long periods. Therefore prior treatment with drugs known to affect the dopamine system may be, at least partially, responsible for the findings. However the biggest problem with all this research is the complete disregard for other possible explanations for increased dopamine activity. Dopamine release is known to be associated with numerous activities and situations that may differ between patients and healthy controls and may account for the difference in dopamine activity

independent of the presence of psychosis. Motor activity and attention have been shown to increase dopamine activity and dopamine is involved in arousal (Berridge 2006). People with acute psychosis are likely to be more aroused and agitated than healthy controls and this may account for increased dopamine activity. None of the recent dopamine-psychosis studies have examined these possible confounders. Nicotine increases dopamine release and people with psychiatric disorders are notoriously heavy smokers. Only one of the recent studies attempted to control for the effects of smoking. It found no evidence of an association between dopamine and smoking, but the study was too small to detect anything but a very large effect (Meyer-Lindenberg et al. 2002). Several studies in animals and humans have found that dopamine is released in response to stress (Adler et al. 2000; Breier 1989; Finlay & Zigmond 1997; Frankenhaeuser et al. 1986; Pruessner et al. 2004; Rauste-von Wright & Frankenhaeuser 1989), although one study with humans using a mild stressor failed to find an association (Montgomery, Mehta, & Grasby 2006). Since patients with psychosis are likely to be in a state of high stress, and research shows their stress hormones are elevated (Pariante et al. 2004; Tandon et al. 1991), it may be that increased dopamine in people with psychosis is a non-specific indication of a state of stress, rather than a specific correlate of psychosis per se. A meta-analytic review of the amphetamine challenge studies was the only report to consider the role of stress in the studies of dopamine in psychosis (Laruelle et al. 1999). It found a statistically significant level of increased anxiety in people with psychosis compared with controls both before and during the procedure.

Overall the evidence in support of the dopamine theory of psychosis or schizophrenia is weak. Much early research was negative and findings that were thought to support the hypothesis turned out to be due to the effects of drug treatment. Recent studies are inconsistent and although some suggest enhanced dopamine activity in some situations, such as following amphetamine ingestion, there has been no allowance made for the numerous other factors that affect dopamine activity. These factors are likely to influence dopamine levels in patients quite independently of their psychotic symptoms. The persistence of the dopamine hypothesis and its recent resurgence in popularity are testimony therefore not to the state of the evidence but more to the need of the psychiatric profession to have medical models of the disorders it is confronted by, particularly ones that provide a medical justification for its treatments.

Is a disease-centred view of neuroleptic drug action justified?

Before moving on to a drug-centred analysis of the effects of neuroleptics, I will conclude this chapter by evaluating the evidence for a disease-centred view of their action according to the headings outlined in Chapter 2.

(1) Is there a demonstrable pathological basis to psychosis/schizophrenia from which the action of 'antipsychotic' drugs can be understood?

Decades of research have failed to produce clear and independent evidence of a dopamine abnormality in people with psychosis or schizophrenia that cannot be attributed to some other cause.

(2) Do rating scales for acute psychosis or schizophrenia reliably measure the manifestations of a particular disease process?

Rating scales used to measure effects of drugs in trials among people with schizophrenia or psychosis contain numerous items that are not confined to these situations or diagnoses and would be likely to respond to any drug with sedative effects. Thus the commonly used Brief Psychiatric Rating Scale (BPRS), which has a total of 18 items, contains items on 'tension', 'uncooperativeness,' 'excitement' and 'hostility'. Each item can score up to 7 points. Differences of 10 points on this scale are usually considered significant. This was the difference between patients treated with clozapine and patients treated with chlorpromazine in the seminal study heralding clozapine as an effective treatment for treatment-resistant schizophrenia, for example (Kane et al. 1988). Similarly of the seven items in the 'positive symptoms' section of the Positive and Negative Syndrome Scale (PANSS), two concern 'excitement' and 'hostility'. Thus decreases in symptom-rating scales after drug treatment do not necessarily indicate improvement in core psychotic symptoms, but may simply reflect sedating effects on various aspects of behavioural disturbance and overarousal. A difference of 10 points on the BPRS could easily reflect sedating effects on behavioural disturbance rather than any specific 'antipsychotic' effect. Use of the 'psychotic symptoms cluster' of the BPRS is a better measure of change in specific symptoms.

(3) Do animal models of psychosis select antipsychotic drugs reliably?

The principle animal model of psychosis has for many years been the hyperactivity and stereotypies induced by stimulant drugs. In animals

and humans prolonged or high-dose stimulants, such as amphetamine, produces repetitive, compulsive movements that are referred to as 'stereotypies'. An example is gnawing movements in rats. Because stimulants can also produce psychosis in humans, it was assumed that a drug which could reduce their motor effects would also have antipsychotic properties. It was observed that dopamine-blocking drugs could reliably reduce stimulants' motor effects and did so more than other sedatives (Pycock, Tarsy, & Marsden 1975). Experiments with animals were also believed to show that dopamine rather than noradrenalin or serotonin was responsible for the effects (Ernst 1967). However the literature on this subject is extremely confusing. Some authors suggest the model detects the extrapyramidal activity of drugs rather than their antipsychotic actions (Pycock, Tarsy, & Marsden 1975), and others regard stereotypy as a model for tardive dyskinesia rather than psychosis (Klawans, Jr. & Rubovits 1972). Some research suggested that noradrenalin might also be implicated (Borison & Diamond 1978; Von Voigtlander & Moore 1973). A recent paper shows that noradrenalin and dopamine are involved in arousal and motor hyperactivity induced by amphetamine (Berridge 2006). Some studies demonstrate that non-neuroleptics like diazepam can also reduce stimulant-induced hyperactivity (Hsieh 1982; Thiebot et al. 1980).

However it is surely not surprising that dopamine-blocking drugs are particularly effective in reducing hyperactivity given their propensity to reduce movement and produce a Parkinson's type picture as described further in the next chapter. Therefore, the model seems to reflect drugs' extrapyramidal action and can be regarded as a screen for drugs with dopamine-blocking activity. In line with this idea, most research shows that second-generation neuroleptic drugs such as clozapine, which have weaker antidopaminergic effects, have relatively weak antistereotypic actions (Costall & Naylor 1976; Tschanz & Rebec 1988).

Therefore the effects of drugs on stimulant-induced stereotypies says nothing about the action of drugs on a disease process, but can be better understood as a reflection of particular drug-induced effects in line with a drug-centred model of drug action.

Numerous other animal models of psychosis have been proposed, but few others have been used routinely for drug screening. The model called the conditioned avoidance response is considered important, however. Smith and colleagues describe the test as follows:

In a typical Conditioned Avoidance Response experiment, a rat is placed in a two compartment shuttle box and presented with a neutral

conditioned stimulus (CS) such as a light or tone, followed after a short delay by an aversive unconditioned stimulus (US), such as a foot shock. The animal may escape the US when it arrives by running from one compartment to the other. However after several presentations of the CS-US pair, the animal typically runs during the CS and before the onset of the US, thereby avoiding the US altogether. Animals treated with low (noncataleptic) doses of antipsychotic drugs fail to perform avoidance responses to the CS, even though their escape response is relatively unaffected.

(Smith et al. 2004, p. 1040)

As this description illustrates the conditioned avoidance response represents the ability of animals to connect to different stimuli. In other contexts, such as research on effects of toxins on the brain, a reduced conditioned avoidance response is taken to indicate an impairment of learning and memory. The initial rationale for using this as a test for antipsychotics was that drugs considered mainly sedative primarily decreased spontaneous motor activity in animals, whereas neuroleptics were thought to selectively suppress the conditioned avoidance response more than motor activity (Cook 1958). However reduction of the conditioned avoidance response is also achieved by many sedatives, albeit with concomitant reduction of motor activity (Arnt 1982; Dielenberg, Arnold, & McGregor 1999) and histamine (Tasaka et al. 1985). Anything that impairs cognitive function including numerous toxins and radioactivity also impair the conditioned avoidance response (Gao, Wang, & Zhou 1999; Shukakidze, Lazriev, & Mitagvariya 2003). Therefore, again, this model provides no evidence of disease specificity but appears, rather, to reflect the particular drug-induced effects of neuroleptics on learning, effects that are shared by other drugs and toxic processes.

(4) Are drugs considered to have non-specific actions inferior?

It is not clear that so-called antipsychotic drugs are superior to other types of drugs with sedative effects but different mechanisms of action. Lithium, benzodiazepines and opium have been shown to be comparable to neuroleptics in the treatment of psychotic states in some studies. The ability of the neuroleptic drugs to reduce the most characteristic symptoms of psychosis such as hallucinations, delusions and thought disorder have often been interpreted as evidence of their specifically antipsychotic or 'antischizophrenic' action (The National Institute of Mental Health Psychopharmacology Service Center Collaborative Study

Group 1964), although benzodiazepines have also been found to reduce these symptoms in most studies where this has been examined.

However showing that neuroleptic drugs were superior to other sedative drugs would not necessarily demonstrate a disease-centred action, since some of the effects induced by neuroleptics may be particularly useful in psychosis. The most obvious of these effects is the capacity of neuroleptic drugs to induce indifference, discussed in more detail in the next chapter. In this respect it is interesting to note that the only RCT of an opiate, another group of drugs that are noted to induce a state of indifference, albeit a rather different one, found that opium was as useful as chlorpromazine for the treatment of a psychotic state. However the data on benzodiazepines, a group of drugs not noted to produce emotional or psychic indifference, suggest that a sedative effect alone may be capable of ameliorating psychotic symptoms.

(5) Do studies with healthy volunteers show different or absent effects?

In the next chapter I describe research in which 'healthy volunteers' have taken neuroleptic drugs. This shows unambiguously that volunteers experience the same range of effects that are seen in patients.

(6) Is the outcome of psychosis/schizophrenia improved by the use of antipsychotic drugs?

Data on the course of schizophrenia have not been able to demonstrate that the introduction of neuroleptic drugs has improved outcome. They may even impair outcome due to harmful effects on the brain or due to the iatrogenic problems encountered when discontinuing psychiatric drugs.

Conclusions

Neuroleptic drugs clearly have different effects from inert placebo. These effects may be beneficial in the short term for some patients with psychotic episodes, in terms of reducing symptoms and getting out of hospital. However some patients with psychosis recover spontaneously, and it is uncertain roughly what proportion gain added benefit from neuroleptic treatment. It is also uncertain whether other sedative drugs might not have the same effects. It is impossible to say whether long-term treatment confers advantages over placebo in terms of relapse prevention because of the potential confounding influence of discontinuation effects in placebo-controlled trials which depress the outcome in the placebo group. Randomised maintenance trials have

also not addressed whether long-term drug treatment affects other aspects of functioning such as social functioning, work performance and quality of life. It is often claimed that neuroleptic drugs have improved the outcome of schizophrenia but it is actually quite difficult to find evidence to support this position. Some evidence even points to the possibility that widespread and long-term drug treatment may make the outcome worse, especially for people who might have done well without drug treatment. Although the bulk of research on neuroleptic drugs has been conducted on the assumption that they act in a disease-centred way, the data produced by this research does not justify this position. A drug-centred model is better able to explain the nature of their effects in people with schizophrenia and psychosis. A drug-centred model also provides a platform from which to weigh up the pros and cons of using such drugs and helps us to judge what role they should have in psychiatric treatment.