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Consensus Statement

The Use of High-Dose Antipsychotic Medication

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Antipsychotic medication is the mainstay of treatment for the functional psychotic illnesses. Such drugs are also referred to as neuroleptics (meaning a drug with both antipsychotic effects and effects on movement) and major tranquillisers. The psychotic illnesses for which they are prescribed include schizophrenia, mania in the course of a bipolar mood disorder, and, more rarely, depression accompanied by psychotic symptoms. These are not uncommon illnesses. At some time during their lives approximately 1% of the population will suffer at least one episode of schizophrenia and a further 1% will suffer at least one episode of mania. During an episode some patients, but by no means all, suffer extreme changes in their thinking, mood and behaviour which can be very distressing to experience and which can make patients a danger to themselves or other people.

Many such patients will be formally detained and may receive treatment without their consent for short periods. Such situations, in the community or in hospital, can be hazardous and require careful management using medication and occasionally electroconvulsive therapy (ECT), together with psychological and social approaches. Ward nurses may be required to supervise the patient individually all day and night for short periods of time. The staff of mental illness units provide skilled care to severely disturbed patients on a daily basis, sometimes at risk to themselves. The majority of patients get better and leave hospital, but those with schizophrenia will generally require maintenance treatment with antipsychotics for some time, perhaps indefinitely, in order to prevent a relapse. For mania the most usual maintenance treatment will be lithium.

In spite of the generally positive outcome of care for psychosis, there has arisen a concern over the last few years that a number of deaths may be occurring in psychiatric patients which might be a result of the medication received rather than a hazard of the severe illnesses from which most such patients suffer (Inquest, *1991–2 Annual Report*). In parallel with this there has been unease that some patients are treated with doses of antipsychotic medication which are above, and sometimes quite markedly above, the recommended guidelines for dose schedules in the *British National Formulary* (*BNF*, published by the Royal Pharmaceutical Society of Great Britain and the British Medical Association).

The Royal College of Psychiatrists has responded to this unease from among its members and others by convening a consensus panel of expert clinicians and pharmacologists to review the use of high doses of antipsychotic drugs. The aim was not to provide comprehensive guidelines for the care of the severely mentally ill or for the routine prescription of antipsychotics, but solely to give an authoritative opinion on the use of 'high doses'. The panel met in December 1992 for one day and each member subsequently had the opportunity to review and comment upon drafts of this report until the contents were agreed by all the participants.

What do the antipsychotic drugs do and how do they work?

This section is written as far as possible in non-technical language, since this statement will be of interest to non-medical members of mental health teams, user groups, those involved in the management, administration and supervision of mental health services and psychiatric trainees. It will not, however, be possible to avoid or fully explain all medical terminology.

Antipsychotic drugs have two main actions. First and foremost they eliminate or reduce the intensity of psychotic experiences – delusions, hallucinations, thought disorder, experiences of passivity, thought alienation, and inappropriate or incongruous mood. This antipsychotic action is usually delayed in onset by one to two weeks from the start of full-dose treatment. It is seldom possible to predict accurately what daily dose the patient will need to achieve such an antipsychotic effect. The therapeutic effect is thought to be closely related to the blockade of dopamine receptors, a property which is shared by all of the conventional antipsychotics. However, this also produces the main side-effects of the antipsychotics which occur in some patients. These are extrapyramidal symptoms such as Parkinsonism, akathisia, dystonia and, later, tardive dyskinesia (although similar involuntary movements can also occur in schizophrenic patients who have never been treated with antipsychotics). The potency of the

1. For the Royal College of Psychiatrists' Consensus Panel.

antipsychotic group of drugs varies, some requiring lower doses to block dopamine receptors than others. They can roughly be divided into low-potency drugs such as chlorpromazine and thioridazine, with dose ranges in the hundreds of milligrams a day, and high-potency drugs such as haloperidol and pimozide, with dose ranges in the tens of milligrams a day or less.

Secondly, antipsychotics have a calming effect, hence the former and now obsolete name, major tranquilliser. This is a more immediate effect and is used extensively in emergencies and during acute treatment before the onset of the antipsychotic action, to relieve the patient's distress or to make safe a dangerous situation. In some rare cases acute disturbance can be very dangerous for the patients as well as the staff and other residents. Furniture is sometimes thrown around, plumbing pulled from the walls, and severe bodily harm can be self-inflicted in states of psychotic excitement. Inadequate treatment is usually at least as dangerous as overzealous treatment in such situations.

Dopamine receptor blockade is less clearly related to the tranquillising effect and some antipsychotics are more sedative or calming than others. Tranquillisation is not specific to the antipsychotics, being shared in certain respects by the anxiolytics, for example benzodiazepines (formerly called minor tranquillisers), although these may act via a different mechanism.

What is a high dose of an antipsychotic?

For nearly all of the antipsychotic drugs, the *BNF* recommends a dose range for routine use. The upper dose is arrived at on the advice of the *BNF* expert medical advisers working mainly from the data sheet produced by the manufacturing company. This is produced after all the available information on the drug has been reviewed by the Committee on the Safety of Medicines and the drug granted a product licence. This review may be the only time when a body of learned opinion has access to the original data. Thus, the upper end of the dose range should be taken seriously. In routine use, exceeding the recommended dose range is likely to risk higher levels of side-effect, eventually exceeding the acceptable risk : benefit ratio.

However, although the lower end of the range of dose is determined by the scientific evidence for efficacy, the upper end is not often so clearly established, and is usually defined by limits of safety. Over the years since the introduction of the older antipsychotics, the upper limit has been increased periodically. For the relatively newer drug pimozide, there was first an increase and then a decrease in the recommended upper dose. The fall resulted from reports of serious cardiac side-effects appearing at higher doses.

The guidance in the *BNF* is in general but not total agreement with other prescribing guidelines. In particular, the BNF does not always agree with the product licence, and in such cases it should be the product licence, as reflected in the data sheet, which should be taken as the advisory maximum limit. However, the differences are minor and for routine clinical purposes the *BNF* (which is a pocket book for rapid reference) will be sufficient.

The dose of antipsychotic a patient will require will depend on several factors, including age; older patients generally require lower doses and often have more side-effects than younger patients. Similarly, in those few adolescents (and even fewer children) who are prescribed antipsychotics, the dose will have to be altered according to size, age and body weight.

Although doses vary from one drug to another, a scheme for rough comparison of 'chlorpromazine equivalents' has been developed, based on limited clinical evidence and in part on the relative potency in blocking dopamine receptors. The literature on equivalents reveals variation, and it may not be possible to express a drug's side-effects and therapeutic effects in one equivalence figure. For example, using this scheme the recommended upper limit in terms of chlorpromazine equivalents varies 10–20-fold between antipsychotics. The less sedative antipsychotics tend to have higher (haloperidol) or no (trifluoperazine) recommended maximum doses. This suggests that upper limits of dose are not related to the postulated mechanism of action of the drug on the symptoms of psychosis, but more to the side-effect profile.

In a highlighted section of the *BNF*, the following statement appears:

> "In some patients it is necessary to raise the dose of an antipsychotic drug above that which is normally recommended. This should be done with caution and under specialist supervision."

Thus the *BNF* guidelines do not constitute a ban on the prescribing of higher than generally recommended doses when carried out with due care by a specialist, and although the term 'advisory maximum limit' is used in this statement and in the *Code of Practice of the Mental Health Act 1983*, the term 'limit' should not be interpreted as fixed for all purposes. The *Code of Practice of the Mental Health Act 1983* (Department of Health, 1990) also recognises that high doses may be used by requiring the responsible medical officer to indicate the dosages on form 38 (consent to treatment) if the patient is on more than *BNF* advisory

maximum limits (page 61, para 16.11). This will need to take account of all antipsychotic drugs if the patient is on more than one.

The members of the consensus panel were aware of these existing prescribing guidelines and agreed to take as a definition of high dose "a total daily dose which exceeds the advisory upper limit for general use" in the *BNF* or product licence. The further recommendations of the consensus group are concerned with the circumstances in which the advised upper limit might be exceeded, ways in which the risk of doing so might be minimised, and alternative treatment strategies to high-dose prescribing.

What are the dangers in using high doses of antipsychotics?

Even at high doses, clinical experience suggests that the antipsychotic group of drugs generally has a good margin of safety. Indeed, Goldney *et al* (1986) found evidence in favour of the safety of regimes of up to 4500 mg chlorpromazine equivalents a day. However, a number of unexpected sudden cardiac deaths have occurred in psychiatric units (Simpson *et al*, 1987; Mehtonen *et al*, 1991) for which antipsychotic drugs have been blamed.

In England in 1990 there were 56 900 in-patient episodes for the mental illness specialities (Department of Health, 1991). This large number indicates that there is likely to be an unexplained death. Goldney *et al* (1986) in Australia calculated the rate of sudden death to be 27 in every 100 000 psychiatric admissions. For comparison, the rate of suicide of psychiatric in-patients was 100 in every 100 000 admissions.

The frequency of sudden death without an ascertainable cause in the general population is not known with any accuracy, hence it is not certain that the rate in psychiatric units is raised over the background level. Too little is known about the characteristics of those who have died in psychiatric units to be absolutely certain that antipsychotics played a part in the death, but where deaths have occurred in young, previously healthy people, the suspicion of involvement of the drug(s) will be stronger. Although media reports tend to describe cases where medication was given, other cases of sudden death in patients not treated by antipsychotics tend not to be reported. Furthermore, for many of the cases reported in the literature or publicised in the press, the antipsychotic was being prescribed at a routine dose. For example, a Finnish study showed a small association between sudden death and routine doses of the low-potency neuroleptic thioridazine (Mehtonen *et al*, 1991). Some practitioners use thioridazine preferentially in the elderly, and so the apparent association might have been due to selection of vulnerable patients rather than a true treatment effect.

The association of the danger of sudden death with high-dose prescription is therefore not firmly established, and more epidemiological evidence is required.

Nevertheless, there are grounds for suspicion of an association since deaths have occurred in young, previously healthy people, and it is known that many antipsychotic drugs have, to differing extents, an action on the heart which can cause cardiac conduction abnormalities and which can lead to sudden death. They block the cell membrane sodium pump which, in cardiac conduction tissue, leads to a slowing of the rate of contraction of the heart. This can be self-limiting, but it can also develop into fatal ventricular fibrillation. It was this effect which led to the lowering of the upper dose of pimozide from 60 to 20 mg per day. There had been 13 sudden unexpected deaths of patients on pimozide, of whom 10 were taking more than 20 mg per day. Seven were under 30 years, most had no previously known cardiac abnormality, and most had been given a rapid increase in the dose (Committee on Safety of Medicines, 1990).

In addition to the effect on cardiac conduction, antipsychotics also have a negative inotropic effect, reducing cardiac output and lowering blood pressure. It has been suggested that a catastrophic fall in blood pressure might have been responsible for some cases of sudden death in those on high doses. Proper hydration can reduce this risk. Chlorpromazine and other older antipsychotics induce more hypotension than the newer, more selective dopamine antagonists.

In very high doses, non-specific neurochemical effects can cause central nervous system depression, respiratory depression, hypoxaemia and sometimes seizures.

Dose-related side-effects also include the extrapyramidal effects of Parkinsonism, dystonia, and akathisia, which are more problematic at very high doses or during rapid escalation of the dose. Prolonged high doses may increase the risk of the subsequent development of tardive dyskinesia, although some argue that the severity of illness determines both the long-term high dose and a liability to tardive dyskinesia independently.

The neuroleptic malignant syndrome appears not to be dose-related, although it may be related to the rate of increase of dose. It consists of hyperthermia, muscular rigidity and autonomic instability, and it is rare and highly unpredictable. Even rechallenge with the same drug or another of the same class does not always cause it to recur. The syndrome can be fatal but, if treated in time, it usually responds to

conservative management and dose reduction. Several other classes of drugs, including anaesthetics, levodopa, carbamazepine and tricyclic antidepressants, have also been implicated in its causation.

Megadoses (more than 2000 mg per day of chlorpromazine equivalents) of antipsychotics have been associated with violent disturbed behaviour, and it may be difficult to decide sometimes whether such behaviour is a result of the illness or the medication (Barnes & Bridges, 1980; Herrera *et al*, 1988).

Why are antipsychotics sometimes used above the advisory maximum dose?

Three treatment situations can be broadly distinguished.

(a) Emergencies

The emergency use of antipsychotics is for their calming effect. In this they are usually very effective at routine doses, although a few patients in each hospital do appear to require relatively high doses. Parenteral injections (intramuscular or intravenous) are often used at this stage for a more rapid effect. While this may be completely justified by the severity of the clinical situation, it is important to be aware of certain dangers. It may not be possible to secure valid consent before the procedure, and the treatment may have to be administered by relatively inexperienced staff while not under immediate specialist supervision. The blood level of the drug will increase rapidly by avoiding first-pass metabolism in the liver, which occurs with oral administration, and the eventual blood level will be much (up to five times) higher. Therefore, the dose should be lower than if it were given orally. It follows that equal doses of medication should not be written up as "p.r.n. (as required) oral or intramuscular", since that instruction does not specify the actual dose of medication to be received by the patient as precisely as is possible. Indeed, when p.r.n. oral medication is used, the prescribing psychiatrist has a duty to review the use of the medication daily in the acute situation to ensure that the maximum daily doses are not being breached or, if they are, it is for good reason and in as safe a manner as possible (see below).

If the patient is very active or involved in violent activity, the rate of absorption from an intramuscular injection will be much faster than in a quiet patient because the rate of blood flow to the muscles is much increased, and this should be taken into account in dose selection. Simpson *et al* (1987) concluded that antipsychotic drugs may interact with autonomic stress as well as violent action to produce cardiac side-effects.

(b) Acute treatment

During acute treatment, in the period before the onset of the antipsychotic action (1 to 2 weeks), there may still be a requirement for a calming effect in the absence of an emergency. However, the dose at which this effect occurs may not be identical to that at which the antipsychotic effect eventually occurs. If the dose of the drug is increased rapidly to induce calming, or in an attempt to achieve antipsychotic effects as quickly as possible, the eventual dose which is reached may inadvertently be higher than necessary for longer-term treatment. If the dose at which the patient has responded is higher than the usual dose range, serious consideration should be given to reducing it as far as possible into the normal range. The consensus panel considered that there was a reluctance among some psychiatrists to reduce the dose of medication once the patient had responded, and that this may contribute to some unnecessary long-term high-dose prescribing. At the lower end of the therapeutic range this reluctance is supported by experimental evidence of higher relapse rates on lower doses (Cookson, 1987), but such evidence is not available for reduction from high to routine dose levels.

Any reductions would have to take into account all of the clinical circumstances, including the patient's and relative's views, the risks to the patient and others should they relapse, and the severity of any side-effects experienced at the time.

(c) Long-term treatment

Treatment resistance

In the longer term, a proportion (10–30%) of patients will be treatment-resistant and show significant residual symptoms of psychosis which impair their everyday activities of living, despite full-dose treatment with two different classes of antipsychotic successively. These symptoms may prevent or impair their full rehabilitation. In such cases the recommended guidelines for dosage are frequently exceeded in the hope that the patient might respond at a somewhat higher dose. This is sometimes successful, since there are individual differences in the dose which patients require and for some this will be above the guidelines in the *BNF*. Where a clinician has experience of this with the same patient in previous episodes of illness it is clearly sensible, in the absence of a response at lower doses, to exceed the suggested limit. However, if the

prescribing policy and the clinical state of the patient are not frequently reviewed, the dose can be increased unchecked, to undesirable levels.

Some psychiatrists have advocated the use of so-called 'megadose' treatment, in which the suggested maximum dose is exceeded deliberately by an order of magnitude (more than 2000 mg per day chlorpromazine equivalents) in an attempt to induce a remission in a severely ill treatment-resistant patient. The evidence for the effectiveness of this practice is described below.

Polypharmacy

There are other reasons why patients are treated with high doses of antipsychotic drugs. A common one is the use of several antipsychotics concurrently. In some instances this is because the first drug chosen was ineffective and it is being changed gradually to a second. In this justifiable case the polypharmacy is temporary. However, several surveys have shown the routine use of more than one antipsychotic. This is against the advice of the *BNF*, which is:

> "Prescribing of more than one antipsychotic at the same time is not recommended; it may constitute a hazard and there is no significant evidence that side-effects are minimised."

The consensus was that such practice is undesirable routinely, although there may be occasional patients for whom it has been proved necessary by experience over several years of dealing with the illness. For example, patients taking an oral antipsychotic may require occasional injections during peaks of psychotic disturbance. This may best be given as another antipsychotic if that would be more comfortable for the patient by virtue of being a more concentrated solution, requiring a lower-volume injection. High-potency antipsychotics may usefully be supplemented periodically by more sedative antipsychotics for episodes of more intense distress.

Resources

The panel had formed the strong impression in the course of their clinical practices that an inadequate in-patient environment commonly contributed to the more frequent use of high doses of antipsychotic drugs in emergency and acute use. Examples included inadequate design of wards for observation, leading to greater concern for safety of other patients. Most importantly the level of trained nursing staff in acute areas is sometimes inadequate. By reducing the time available to talk with patients to form relationships, understaffing raises the level of anxiety among patients and staff. When nurses feel that the situation is unsafe they will often ask the doctor to write up more sedative medication for a moderately disturbed patient. If that fails they may ask that the patient is transferred to a more secure unit. The panel heard that it is common for doctors in semisecure facilities to accept disturbed patients on very high doses of antipsychotics and then, in their better-staffed, more secure environment, to be able to reduce the dose quite rapidly. There was also grave concern that nurse training no longer gives sufficient emphasis to the nursing management of severe illness and of the disturbed patient.

In some mental health services, the transfer of scarce revenue from in-patient units to community developments (as opposed to the use of additional funds for such purposes) has led to inadequacy of the in-patient environment and discriminates against the most severely mentally ill. Decreasing numbers of acute beds for mental illness increases the pressure to discharge patients early and leads to pressure to increase doses rapidly. Patients must be given time to recover. This is an essential ingredient of any therapeutic plan, but time is a scarce commodity in today's Health Service.

What is the evidence for benefit from high-dose antipsychotic medication?

In the last 20 years, the use of high doses has tended to increase but the evidence for efficacy in such high doses is limited. So-called megadose treatment has been used in otherwise treatment-resistant patients. Controlled studies comparing standard with high doses in such resistant cases have failed to show superior effectiveness of the megadose regime (e.g. Prien & Cole, 1968; Kane, 1987). In these studies a similar proportion of each group improved (Itil *et al*, 1970; Quitkin *et al*, 1975; McClelland *et al*, 1976; Dencker *et al*, 1978; McCreadie *et al*, 1979; Bjorndal *et al*, 1980). Thus, additional time on standard doses may be sufficient therapy in some cases, suggesting that the classification as treatment-resistant was premature, again highlighting the need to allow time for recovery. No specific illness characteristics predict response to megadoses (Little *et al*, 1989). However, schizophrenic patients under 40 and hospitalised for less than 10 years may be those most likely to benefit (Gardos *et al*, 1973; McCreadie *et al*, 1979). When patients who appeared to respond to megadose treatment were followed up, maintenance treatment with standard doses appeared to be sufficient to maintain the remission (Bjorndal *et al*, 1980; McCreadie & MacDonald, 1977; Cookson *et al*, 1983).

The rationale for such treatment is that very high doses may be required in a few patients in order to

block dopamine receptors satisfactorily. It is now possible to visualise the amount of dopamine receptor blockade caused by antipsychotics in the living patient using a technique known as positron emission tomography (PET). This has shown that near maximal receptor occupancy (70–90%, beyond which an increase is difficult to produce) occurs at modest doses (chlorpromazine and thioridazine at 300–400 mg, haloperidol and pimozide at 4–12 mg, fluphenthixol at 6 mg daily; Farde *et al*, 1992). Patients who were resistant to normal doses of antipsychotics still had 80–85% of their dopamine receptors occupied. This was indistinguishable from those who responded to such drugs (Wolkin *et al*, 1989*a*). This raises doubts about the pharmacological rationale of raising doses to megadose levels. Furthermore, the maximum receptor occupancy occurred at blood levels of antipsychotics (10 ng per ml of haloperidol) which are achieved by quite modest daily doses (Wolkin *et al*, 1989*b*), suggesting that pharmacokinetic factors play a relatively small part in treatment resistance. Nevertheless, the dopamine theory of the action of antipsychotics may not be the whole story. Clozapine is atypical, showing high therapeutic efficacy at low dopamine receptor occupancy (Farde *et al*, 1992; Pilowsky *et al*, 1992*b*). This raises the possibility that the typical antipsychotics, when they work at high doses may do so via a different mechanism, perhaps one which is unknown. Nevertheless, the point remains that both the rationale for the use of megadoses and the scientific evidence for their effectiveness are limited.

What are the alternatives to high doses of antipsychotics in treatment-resistant patients?

Emergency

In emergency use for rapid tranquillisation, benzodiazepines have been reported to be an effective treatment in combination with lower doses of antipsychotics (*Drug and Therapeutics Bulletin*, 1991). Experience shows that relatively modest doses of a benzodiazepine, such as 2–4 mg lorazepam per day, in combination with a moderate dose of an antipsychotic, such as 10–20 mg haloperidol, can be very effective. Although the use of one drug (the antipsychotic) for two actions may be appropriate when used at routine doses, at high doses the risk : benefit ratio may change, and it may be safer to use two drugs, each within their normal therapeutic range and each for their target effect – an antipsychotic drug for its eventual antipsychotic action and a benzodiazepine for its short-term sedation. However, the benzodiazepines also have dangers attached to their use. Patients with respiratory difficulties should be treated with caution, all patients should be considered for gradual withdrawal at the earliest opportunity to avoid an unnecessary risk of dependence, and all patients should be observed for the rare paradoxical effect of disinhibition (Dietch & Jennings, 1988).

A newer strategy has been to use a medium-term injectable antipsychotic (zuclopenthixol acetate is the only available product). Some psychiatrists find this to be effective, and without the repeated intramuscular injections required when using shorter-acting drugs, but there are also potential dangers of injecting a previously untreated patient with a drug that has a long half-life. It should therefore be used only in patients who have previously tolerated antipsychotics well, unless the circumstances are exceptional and can justify the potentially increased risk which will be presented.

Patients who remain somewhat disturbed may require special nursing supervision until they begin to improve.

Acute treatment

In this situation there may not be an immediate need to sedate the patient but the drugs have not yet had their antipsychotic effect. It is recommended that the dose of the medication should be increased only gradually (e.g. weekly), so as not to exceed the dose necessary to treat the psychosis, since the antipsychotic effects generally take one to two weeks to become evident. If the patient is responding slowly and there is some urgency in the clinical situation, other methods of inducing a remission should also be considered. ECT can be effective as a treatment in acute, positive-symptom psychosis (Taylor & Fleminger, 1980). It is regarded to be as safe as antipsychotic medication in higher doses, and it can rapidly bring psychotic symptoms under control, but should be replaced by antipsychotics to maintain the effect once it has been achieved.

Treatment-resistant patients

For patients who have failed to respond to two antipsychotics at full dose, there remains a range of options other than exceeding the recommended limit.

(a) Review the diagnosis. Is the patient really psychotic? Has an organic cause been excluded? Is there a possibility that illicit drug use is exacerbating the psychosis? If so, a urine test for a drug screen might be helpful. Are the

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remaining symptoms 'negative symptoms' and therefore less likely to respond?

(b) Has a therapeutic blood level been achieved? Is the patient failing to take the medication? Even with close observation, about 10% of in-patients have no trace of the prescribed medication in their blood and poor compliance should always be considered as a cause of non-response.

(c) Has treatment been carried on for long enough? Are there early signs of improvement which could encourage persistence for a little longer? Would a temporary increase in nurse staffing reduce the level of disturbance on the ward until this takes place? Allowing sufficient time for recovery to take place before changing a treatment plan is essential.

(d) Consider reducing the dose of the antipsychotic slowly for a trial period. Some studies suggest a curvilinear dose–response relationship, possibly because of inducing iatrogenic negative symptoms at very high dose (Baldessarini *et al*, 1988). Rarely the anticholinergic effects of the antipsychotics may induce a toxic psychosis which will improve with dose reduction.

(e) Consider adverse social and psychological factors which may be perpetuating the psychosis, including family factors (high expressed emotion), the ward environment, and disturbances caused by other patients.

(f) Consider specific psychological interventions aimed at target symptoms, such as hallucinations, or at improving the level of social role functioning (i.e. rehabilitation).

(g) Consider other targeted drug treatments such as lithium, antidepressants or carbamazepine if there are severe mood symptoms, agitation or overexcitement.

(h) Clozapine has superior efficacy over typical antipsychotics in treatment-resistant patients and may have beneficial effects on negative symptoms (Kane *et al*, 1988; Baldessarini & Frankburg, 1991). Extrapyramidal side-effects are usually mild, but a lowered white blood cell count is more likely and necessitates a complex monitoring procedure and withdrawal in about 3.5% of patients. About 0.8% of patients develop agranulocytosis. Other side-effects include sedation, seizures, myoclonus and hypersalivation.

Guidelines and suggestions

These guidelines are intended to be informative and facilitatory rather than prescriptive. The complexity of treating patients with severe psychosis is such that the responsibility for the advice given to the patient and for the final decision on the administration of medication should always rest with the consultant psychiatrist within the constraints of statutory and common law. Exceeding the usual recommended dose should always be done with caution. Otherwise the patient may be put at risk and the way to litigation opened. The *Drug and Therapeutics Bulletin* (1992) states:

> "doctors may prescribe unlicensed medicines or depart from the prescribing directions given in the data sheet of licensed medicines. Such prescribing should be done knowingly, and where possible the position explained to the patient in sufficient detail to allow them to give informed consent. Prescribing outside the licence alters and probably increases the doctor's professional responsibility."

This guidance protects the right to treatment of patients who do require higher doses for effective treatment. The only proper basis on which that can be decided is by a careful assessment of each individual patient by a fully trained psychiatrist.

A junior trainee psychiatrist (SHO or registrar without MRCPsych) is not considered to be sufficiently qualified to take a decision to raise the dose of antipsychotics (or the combined dose of using more than one) above the recommended upper limit. This applies particularly in the emergency and acute situation where junior doctors on call appear regularly to exceed *BNF* doses (Pilowsky *et al*, 1992*a*).

Although the *BNF* dosage guidelines constitute advice for the generalist more than the specialist, there is widespread use by psychiatrists of doses above and sometimes well above the suggested upper end of the range. The panel considered that it was unlikely that this practice was always fully justified and that psychiatrists will wish to consider carefully the *BNF* guidelines.

If a decision is being considered to exceed the recommended upper limit the following precautions are offered for the guidance of the practitioner.

(a) (i) Endeavour to discuss with the multidisciplinary team and where possible with the patient and their family or advocate the reasons for the treatment, including a consideration of the alternatives. Often this is not possible in the middle of the night.

(ii) Where possible, obtain 'valid' (proper or real) consent and for detained patients ensure compliance with the provisions of Part IV of the Mental Health Act 1983.

(iii) Within the multidisciplinary team all prescribing decisions are the responsibility of the consultant psychiatrist.

(iv) Keep a thorough record of the decision and the reasoning which had led to it, including the details of previous treatment and the patient's mental and physical state.

(v) It might be prudent in some circumstances to discuss the treatment with another consultant psychiatrist, but a second opinion, while prudent, is not mandatory outside the statutory requirements (Royal Australian and New Zealand College of Psychiatrists, 1991).

(b) Are there any relative contraindications to high-dose therapy? These include: coexisting medical conditions such as cardiac disorders, especially a history of myocardial infarction or arrhythmias or an abnormal electrocardiogram (ECG); old age; and hepatic or renal impairment. Furthermore, those who are obese, and heavy users of alcohol or tobacco may be at higher risk.

(c) Are there any greater risks due to drug interactions? These might include tricyclic antidepressants and antihistamines. If the patient has hay fever he/she should be warned not to buy terfenadine (Triludan) or astemizole (Hismanal) over the counter since they can be associated with cardiac arrhythmias. Diuretics can produce fluid depletion and electrolyte imbalances, aggravating any tendency to cardiac arrhythmias or hypotension.

(d) When possible, carry out an ECG to exclude long 'QT' syndromes. Repeat the ECG every one to three months while the dose remains high. If a prolonged QT interval develops reduce the dose.

(e) During high-dose treatment it would make sense to increase the dose of medication slowly. Increments should generally only be made at intervals of at least one week. This is thought to reduce the risk of neuroleptic malignant syndrome and will allow time for the effect of each new dose to be observed before proceeding to the higher dose. Emergencies may necessitate that this guideline cannot be followed.

(f) Carry out regular checks on pulse, blood pressure and temperature. Check hydration (by physical examination and/or urea and electrolytes) to avoid electrolyte imbalances and hypotension.

(g) Review progress regularly. The procedure should be treated as a limited course and the dose reduced to accepted levels after three months if there has been no improvement (Hirsch & Barnes, 1994).

Further recommendations

Regardless of the association between treatment and sudden deaths in psychiatric hospitals, all psychiatrists should have experience in resuscitation and know how to use the resuscitation equipment in the hospital, most frequently to be found in the ECT suite. Each hospital or ward should have an appropriate procedure for dealing with cardiac arrest.

The lack of clear information about sudden unexplained deaths in psychiatric hospitals and the unease surrounding them suggests that consideration should be given to establishing a study under the auspices of the College's Psychopharmacology Subcommittee. In the meantime all sudden unexpected deaths which might be associated with antipsychotic prescribing should be reported using the yellow-card scheme of the Committee on Safety of Medicines.

Psychiatric units should audit their use of high doses of antipsychotic drugs using this consensus statement to set standards. And individual units might wish to develop their own treatment protocols for treatment-resistant patients and the emergency management of psychotic excitement.

Special problems

Learning disabilities

Those patients with learning disabilities and mental illness pose particular problems. In this group there are special difficulties of communication which make the diagnosis of psychosis a specialist task. Furthermore, some specialists find that non-psychotic behavioural disturbance may also respond to antipsychotics, and large doses are sometimes used for this purpose. In the presence of cerebral dysfunction or damage, the patient may be particularly sensitive to side-effects, so the threshold for 'high dose' is lower. Recognition of these side-effects is not always straightforward. The medical history may be incomplete so the presence of cardiac and renal problems may not be appreciated. A relatively high proportion of patients have epilepsy and are taking anti-epileptics. Antipsychotic medication reduces the seizure threshold, increasing the required dose of the anti-epileptic. There are problems with consent to treatment and the evaluation of treatment response. As far as possible the guidelines described above should be adhered to. Further guidance can be found in Einfeld (1990).

The use of high dose antipsychotic medication in children and adolescents

Major psychotic illnesses occur in adolescence and may present similar resistance to treatment to that which occurs in adults. However, there are some special considerations that need to be taken into account before high-dose medication is used in young people.

(a) Acute psychosis in young people can present in a dramatic way, with high levels of acting out and antisocial behaviour. It is important that adolescent reactions to stress should not be confused with behaviour that is driven by psychotic processes. High-dose medication may only serve to make the adolescent feel more distressed and lead to further acting out.

(b) Psychotic disorders with an onset in adolescence may be both serious and unresponsive to medication. Nevertheless, the natural history of early-onset psychosis is for the first few episodes to remit spontaneously. Thus the primary treatment goal is to limit the feelings of distress and to protect the young person from harm during the period of illness. The total removal of symptoms is not always a helpful target to aim for.

(c) High-dose antipsychotic medication should rarely be necessary in children and adolescents. Since the illness is likely to be of recent onset, alternative treatment approaches need to be fully explored before considering high dosage. Young people are particularly responsive to their environment and every effort needs to be made to optimise structure of their everyday lives and the quality of their care.

(d) Many aspects of children's and adolescents' behaviour can be disturbing and challenging. High-dose antipsychotic medication should not be used simply to make carers feel less challenged or as a substitute for good quality care that may require high levels of staffing.

(e) Organic brain disorders that are the direct cause of psychotic reactions or are associated with functional psychosis can be made worse by high-dose medication. Side-effects are also more common and more likely to be serious in the presence of organic brain dysfunction.

(f) Antipsychotic medication at any dosage is best avoided in non-psychotic children and adolescents unless there is overwhelming evidence that the child would be exposed to unacceptable risk or intolerable distress without this form of treatment.

It is concluded that high-dose antipsychotic medication has a place in the range of treatments of resistant psychotic states in young people. But this is a rare occurrence, and there are many specific considerations that must be taken into account before this form of treatment is instituted. Issues of consent in children under 16 years are important. It is also essential to try to obtain agreement and support for the use of high-dose medication from all those involved in the care of the young person.

Appendix 1. *BNF* advisory maximum daily doses

Oral antipsychotics

Chlorpromazine	1000 mg
Benperidol	1.5 mg
Clozapine	900 mg
Perphenazine	24 mg
Pimozide	20 mg
Prochlorperazine	100 mg
Promazine	800 mg
Droperidol	120 mg
Flupenthixol	18 mg
Fluphenazine	20 mg
Haloperidol	100 mg
	(occasionally 200 mg)
Loxapine	250 mg
Methotrimeprazine	1000 mg
Oxypertine	300 mg
Pericyazine	300 mg
Remoxipride	600 mg
Sulpiride	2400 mg
Thioridazine	800 mg
Trifluoperazine	None
Triluperidol	8 mg
Zuclopenthixol acetate (intramuscular)	400 mg (per course)
Zuclopenthixol dihydrochloride (oral)	150 mg

Depot injections: maximum weekly dose

Flupenthixol decanoate	400 mg
Fluphenazine decanoate	50 mg
Fluspirilene	20 mg
Haloperidol decanoate	300 mg (every 4 weeks)
Pipothiazine palmitate	200 mg (every 4 weeks)
Zuclopenthixol decanoate	600 mg

Appendix 2. Participants

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Ms M. Mitchell, *Manic Depression Fellowship*
Mr B. McGinnis, *Royal Society for Mentally Handicapped Children and Adults*
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References

BALDESSARINI, R. J., COHEN, B. M. & TEICHER, M. H. (1988) Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Archives of General Psychiatry*, **45**, 79–90.

—— & FRANKENBURG, F. R. (1991) Clozapine, a novel antipsychotic agent. *New England Journal of Medicine*, **324**, 746–754.

BARNES, T. R. E. & BRIDGES, P. K. (1980) Disturbed behaviour induced with high dose antipsychotic drugs. *British Medical Journal*, **281**, 274–275.

BJORNDAL, E., BJERRE, M., GERLACH, J., *et al* (1980) High dose haloperidol therapy in chronic schizophrenic patients. A double-blind study of clinical response, side effects, serum haloperidol and serum prolactin. *Psychopharmacology*, **67**, 17–23.

COOKSON, I. B. (1987) The effects of a 50% reduction of cis(z)-fluphenthixol decanoate in chronic schizophrenic patients maintained on a high dose regime. *International Clinical Psychopharmacology*, **2**, 141–149.

——, MUTHU, M. S., GEORGE, A., *et al* (1983) High dose neuroleptic treatment of chronic schizophrenic patients. *Research Communications in Psychology and Behaviour*, **4**, 305–316.

COMMITTEE ON THE SAFETY OF MEDICINE (1990) Cardiotoxic effects of pimozide. *Current Problems*, No. 29.

DENCKER, S. J., JOHANSSON, R., LUNDIN, L., *et al* (1978) High doses of fluphenazine enanthate in schizophrenia: a controlled study. *Acta Psychiatrica Scandinavica*, **57**, 405–414.

DEPARTMENT OF HEALTH (1990) *Code of Practice of the Mental Health Act 1983*. London: HMSO.

—— (1991) Personal social services: provision for people with mental illness in England 1980–90. *Department of Health Statistical Bulletin*, **3**, 91.

DIETCH, J. T. & JENNINGS, R. K. (1988) Aggressive dyscontrol in patients treated with benzodiazepines. *Journal of Clinical Psychiatry*, **49**, 184–188.

DRUG AND THERAPEUTICS BULLETIN (1991) Management of behavioural emergencies. *Drug and Therapeutics Bulletin*, **29**, 62–64.

—— (1992) Prescribing for unlicensed drugs or using drugs for unlicensed indications. *Drug and Therapeutic Bulletin*, **30**, 97–99.

EINFELD, S. (1990) Guidelines for the use of psychotropic medication in individuals with learning disability. *Australian and New Zealand Journal of Developmental Disabilities*, **16**, 71–73.

FARDE, L., NORDSTROM, A. L., WIESEL, F. A., *et al* (1992) Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Archives of General Psychiatry*, **49**, 538–544.

GARDOS, G., COLE, J. O. & ORZACK, M. H. (1973) The importance of dosage in antidepressant drug administration, a review of dose-response studies. *Psychopharmacologia*, **29**, 221–230.

GOLDNEY, R. D., SPENCE, N. D. & BOWES, J. A. (1986) The safe use of high dose neuroleptics in a psychiatric intensive care unit. *Australian and New Zealand Journal of Psychiatry*, **20**, 370–375.

HERRERA, J. N., SRAMEK, J. J., COSTA, J. F., *et al* (1988) High potency neuroleptics and violence in schizophrenia. *Journal of Nervous and Mental Disease*, **176**, 558–561.

HIRSCH, S. R. & BARNES, T. R. E. (1994) Clinical use of high-dose neuroleptics. *British Journal of Psychiatry*, **164**, 94–96.

ITIL, T., KESKINER, A., HEINEMANN, L., *et al* (1970) Treatment of resistant schizophrenics with extreme high dose fluphenazine hydrochloride. *Psychosomatics*, **11**, 456–463.

KANE, J. M. (1987) Treatment of schizophrenia. *Schizophrenia Bulletin*, **13**, 133–156.

——, HONIGFELD, G., SINGER, J., *et al* (1988) Clozapine for the treatment resistant schizophrenic: a double blind comparison with chlorpromazine. *Archives of General Psychiatry*, **45**, 789–796.

LITTLE, K. Y., GAY, T. L. & VORE, M. (1989) Predictors of response to high dose antipsychotics in chronic schizophrenics. *Psychiatry Research*, **30**, 1–9.

MCCLELLAND, H. A., FARQUHARSON, R. G., LEYBURN, P., *et al* (1976) Very high dose fluphenazine decanoate: a controlled trial in chronic schizophrenia. *Archives of General Psychiatry*, **33**, 1435–1439.

MCCREADIE, R. G. & MACDONALD, I. M. (1977) High dose haloperidol in chronic schizophrenia. *British Journal of Psychiatry*, **131**, 310–316.

——, FLANAGAN, W. L., MCKNIGHT, J., *et al* (1979) High dose flupenthixol decanoate in chronic schizophrenia. *British Journal of Psychiatry*, **135**, 175–179.

MEHTONEN, O.-P., ARANKO, K., MALKONEN, L., *et al* (1991) A study of sudden death associated with the use of antipsychotic or antidepressant drugs. *Acta Psychiatrica Scandinavica*, **84**, 58–64.

PILOWSKY, L. S., RING, H., SHRINE, P. J., *et al* (1992*a*) Rapid transquillisation, a survey of emergency prescribing in a general psychiatric hospital. *British Journal of Psychiatry*, **160**, 831–835.

———, COSTA, D. C., ELL, P. J., *et al* (1992*b*) Clozapine, single photon emission tomography and the D_2 dopamine receptor blockade hypothesis of schizophrenia. *Lancet*, **340**, 199–202.

PRIEN, R. F. & COLE, J. O. (1968) High dose chlorpromazine therapy in chronic schizophrenia. *Archives of General Psychiatry*, **18**, 482–495.

QUITKIN, F., RIFKIN, A. & KLEIN, D. F. (1975) Very high dosage vs standard dosage fluphenazine in schizophrenia. *Archives of General Psychiatry*, **32**, 1276–1281.

ROYAL AUSTRALIAN AND NEW ZEALAND COLLEGE OF PSYCHIATRISTS (1991) *Practice guidelines number 4. General Statement Concerning the Use of Medication Dosages Outside Normal Clinical Practice*. Practice Guideline No. 4. Sydney: Royal Australian and New Zealand College of Psychiatrists.

SIMPSON, G. M., DAVIS, J., JEFFERSON, J. W., *et al* (1987) Sudden deaths in psychiatric patients: the role of neuroleptic drugs. American Psychiatric Association task force report, 27. Washington, DC: APA.

TAYLOR, P. J. & FLEMINGER, J. J. (1980) ECT and schizophrenia. *Lancet*, *i*, 1380–1382.

WOLKIN, A., BAROUCHE, F., WOLFE, A. P., *et al* (1989*a*) Dopamine receptor blockade and clinical response: evidence for two biological subgroups of schizophrenia. *American Journal of Psychiatry*, **146**, 905–908.

———, BRODIE, J. D., BAROUCHE, F., *et al* (1989*b*) Dopamine receptor occupancy and plasma haloperidol levels. *Archives of General Psychiatry*, **46**, 482–483.

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