

Consensus statement on high-dose antipsychotic medication

Council Report CR138
May 2006

Royal College of Psychiatrists
London

Approved by Council: October 2005

Due for review: 2008

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Executive summary and recommendations

The terms of reference and remit of the Working Group were to review and update the consensus statement on the use of high-dose antipsychotic medication (Council Report CR26) published by the Royal College of Psychiatrists in October 1993.

This revised statement reflects the consensus opinion of the members of the Working Group. It addresses the use of high-dose antipsychotic medication only in adult mental health services, and not other psychiatric services such as child and adolescent, elderly, and learning difficulties. Recommendations are made in respect of clinical practice for those involved professionally, as part of a multidisciplinary team or individually, with people receiving antipsychotic medications. Guidance on implementing these recommendations is provided. The issue of compatibility between the proposed recommendations and current relevant treatment guidelines, including the National Institute for Clinical Excellence (NICE) Schizophrenia Guideline (National Institute for Clinical Excellence, 2002) are discussed.

Recent prevalence studies reveal that up to a quarter of psychiatric in-patients are prescribed a high dose of antipsychotic medication, with the highest prevalence figures being found in psychiatric intensive care units, rehabilitation wards and forensic units. There are only limited data on the frequency of prescription of high-dose antipsychotics in psychiatric patients receiving care in the community.

The results of the published trials of high-dose antipsychotic medication for treatment-resistant schizophrenia provide no evidence to support such a strategy. On the basis of current evidence, high-dose prescribing, either with a single agent or combined antipsychotics, should rarely be used and then only for a time-limited trial in treatment-resistant schizophrenia after all evidence-based approaches have been shown to be unsuccessful or inappropriate.

Antipsychotic drugs are commonly prescribed in combination for those with a psychotic illness who have shown a lack of a satisfactory response to a single antipsychotic. While the limited research conducted fails to demonstrate convincing benefits for such a strategy, there is evidence that combined antipsychotics are associated with an increased risk of adverse effects and pharmacokinetic interactions. However, there is some support for the addition of a second antipsychotic to clozapine in people with treatment-resistant schizophrenia for whom clozapine alone has proved insufficiently effective.

High-doses of antipsychotic medication are sometimes used for rapid tranquillisation, persistent aggression and to reduce the risk of relapse. However, there is a paucity of research evidence specifically examining the efficacy and safety of high doses for rapid tranquillisation. There is no convincing evidence base for the use of high-dose antipsychotic medication

in the management of persistent aggression associated with psychosis, or for relapse prevention in psychosis. Relapse prevention studies have tended not to study high-dosage regimens, but rather have examined standard-dose regimens, and low-dose and intermittent, targeted treatment strategies.

A possible link has been postulated between antipsychotic drugs and ventricular tachycardia and sudden death but no consensus has been achieved on the frequency of these events, the contribution of high dosage, or even whether a true causal association exists. To reduce the risk of arrhythmia, all patients should be assessed (including electrocardiography) for cardiovascular disease prior to the institution of antipsychotic drug therapy. Periodic monitoring of the electrocardiogram (ECG), and electrolytes during therapy is advocated when high-dose antipsychotic drug treatment is used (see p. 25).

RECOMMENDATIONS

- 1 The Consensus Working Group recommends the following definition for high dose: a total daily dose of a single antipsychotic which exceeds the upper limit stated in the *British National Formulary (BNF)* (published by the British Medical Association & Royal Pharmaceutical Society of Great Britain) or a total daily dose of two or more antipsychotics which exceeds the *BNF* maximum using the percentage method (see chapter on Definition of high dose).
- 2 Current evidence does not justify the routine use of high-dose antipsychotic medication in general adult mental health services, either with a single agent or combined antipsychotics.
- 3 If high doses are to be used in an individual case, this should only be after evidence-based strategies have failed, and as a carefully monitored therapeutic trial.
- 4 The decision to prescribe high dose (of either an individual agent or through combination) should be taken explicitly and should involve an individual risk–benefit assessment by a fully trained psychiatrist. This should be undertaken in consultation with the wider clinical team and the patient and a patient advocate, if available, and if the patient wishes their presence.
- 5 Supplementary prescribers should not make the decision to proceed to the use of high dose.
- 6 The decision to prescribe high dose should be documented in the case notes, including the risks and benefits of the strategy, the aims, and when and how the outcome will be assessed.
- 7 Dose escalation should be in relatively small increments and allow adequate time for response, and this includes prescribing once the high-dose threshold has been passed.
- 8 Careful watch should be kept on the dosage in terms of total percentage arising from drug combinations, and the use of PRN (as required) medication. Local systems should be developed to alert the responsible psychiatrist/clinical team to patients currently being administered or at risk of receiving high doses.

- 9 The use of PRN medication should be kept under regular review, with training of the clinical team and psychiatric trainees in the use of PRN and alternative ways of dealing with acute patient agitation. Staff administering PRN should be aware of its potential to raise the total daily dose of antipsychotic above the high-dose threshold.
- 10 The possible contraindications to high dose, for the drug(s) in the patient concerned should be considered before prescribing a high dose.
- 11 Consider possible drug interactions when prescribing high-dose antipsychotic medication.
- 12 Before prescribing high-dose antipsychotics carry out an ECG to establish a baseline, and exclude cardiac contraindications, including long QT syndromes. An ECG should be repeated after a few days and then every 1–3 months in the early stages of high-dose treatment. The ECG should be repeated as clinically indicated.
- 13 Services should be structured, managed and resourced to preclude or minimise the perceived need for high dose (see chapters on Responsibilities for prescribing, administering and dispensing and Service implications).
- 14 Each service should establish the audit of antipsychotic doses as a matter of routine practice.

AGGRESSION WITH PSYCHOSIS AND RAPID TRANQUILLISATION

- 15 Therapeutic strategies, such as de-escalation techniques and rapid tranquillisation using benzodiazepines and/or antipsychotic drugs within recommended dosage range, are recommended (see National Collaborating Centre for Nursing and Supportive Care, 2005 and Royal College of Psychiatrists College Research Unit, 1998).
- 16 In cases of acute violence and emergency tranquillisation the dose of antipsychotic used may be minimised by:
 - constantly reviewing the use of alternative/adjunctive strategies (de-escalation and aggression management techniques, benzodiazepines)
 - providing (or transferring the patient to) a suitable environment, with adequate numbers of appropriately skilled staff
 - allowing sufficient time for clinical response between dosage increments.
- 17 If high-dose antipsychotic treatment has been used, it is particularly important that the routine monitoring of a sedated patient is carried out, with particular attention to regular checks of pulse, blood pressure, respiration, temperature and hydration. ECGs should be carried out frequently during dose escalation, if and when possible.
- 18 During acute violence or emergency tranquillisation avoid parenteral antipsychotics if possible, but if used, ECG monitoring or regular ECGs should be performed.

TREATMENT-RESISTANT PSYCHOSIS

- 19 A fully trained psychiatrist should carefully and regularly assess patients whose illnesses have proved unresponsive to conventional doses of antipsychotics (for example, treatment-resistant schizophrenia). The possible contribution to poor response of non-adherence to prescribed medication should be considered, including consideration of plasma drug assay.
- 20 Local protocols, based on national guidelines, should be developed for the clinical management of cases of treatment resistance and of imminent violence and aggression.
- 21 Before resorting to a high dose of antipsychotic medication, evidence-based strategies for treatment resistance should be exhausted, including use of clozapine.
- 22 The use of high dose should be treated as a limited therapeutic trial in treatment-resistant schizophrenia, and the dose reduced back to conventional levels after a 3-month period unless the clinical benefits outweigh the risks.

The recommendations above are based on the literature reviewed in the document and the consensus view of the Working Group. A systematic review of high-dose medication in the clinical trial literature was outside the remit and capacity of the Working group, but should be considered, and would form an appropriate basis for future clinical guidelines in this area.

Definition of high dose

ANTIPSYCHOTIC MONOTHERAPY

In order to receive a marketing authorisation (previously known as a product licence), extensive preclinical (animal) and clinical (human) studies have to be completed. The findings are submitted to the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, or the European Medicines Evaluation Agency (EMA) if a pan-European marketing authorisation is being sought. A panel of experts carefully considers efficacy and safety data and, if acceptable, a marketing authorisation is granted. The summary of product characteristics outlines the conditions of the marketing authorisation, which include the dosage range that has been demonstrated to give the best balance between the desired clinical effect and unwanted side-effects. The Working Group agreed that for a single antipsychotic, a high dose would be one that *exceeded the* maximum dose stated in the manufacturer's summary of product characteristics for that drug.

The summaries of product characteristics for the older, first-generation ('typical' or 'conventional') antipsychotics often refer to broader clinical indications and wider dosage ranges than the summaries of product characteristics for drugs that have been marketed in the past 10 years or so. As new data emerge, the dosage recommendations in the summary of product characteristics may change to reflect this new knowledge. For example, the dosage recommendations in the summary of product characteristics for oral haloperidol have all been revised downwards over the past few years. A maximum dose of 30mg/day in treatment-resistant schizophrenia has replaced the 240mg/day 'in extreme cases' that was previously authorised. Prescribing a dose higher than is stated in the summary of product characteristics is likely to exceed the acceptable risk-benefit ratio for the drug and constitutes off-label use. The prescriber (along with the pharmacist and nurse), not the manufacturer, assumes responsibility for any harm to the patient (see chapter on Responsibilities for prescribing, administering and dispensing).

The dosage recommendations in the *BNF* primarily reflect the summary of product characteristics, although expert clinical opinion can also influence the advice given. For example, in edition 20 of the *BNF* (British Medical Association & Royal Pharmaceutical Society of Great Britain, 1990 - September), when the use of high-dose antipsychotics was accepted clinical practice, a highlighted section was added. It contained the following statement: 'In some patients it may be 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'. By the time of publication of edition 28 (British Medical Association & Royal Pharmaceutical Society of Great Britain, 1994 - September), more was understood about

the pharmacology of the antipsychotics, the use of clozapine in treatment-refractory schizophrenia had been established and the Royal College of Psychiatrists (1993) had published its consensus statement on the use of high-dose antipsychotic medication. This highlighted text was removed. It was replaced by a summary of the good practice points relating to the prescribing and monitoring of high-dose regimens.

Summaries of product characteristics can change at any time in line with new data and they can also be idiosyncratic. For example, all brands of sulpiride have an upper dosage limit of 2400 mg/day with the exception of Sulpitol® (Pharmacia), which has an upper limit of 1800 mg/day. This is not reflected in the 50th edition of the *BNF* (British Medical Association & the Royal Pharmaceutical Society of Great Britain, 2005). The *BNF* is revised every 6 months and cannot therefore always reflect the content of every summary of product characteristics. Further, for modern antipsychotics, the *BNF* may not always reflect the refinement of their use in psychiatric practice and the results of recent clinical trials. Despite these limitations, the *BNF* is still the most user-friendly and widely used source of basic prescribing information. Doses that are above the maximum stated in the *BNF* ('above *BNF* limits') can therefore be described as high dose.

COMBINED ANTIPSYCHOTICS/ANTIPSYCHOTIC POLYPHARMACY

The concurrent use of two or more antipsychotics may result in an individual being exposed to a high antipsychotic dose. There are two methods for calculating the cumulative antipsychotic dose:

- by converting the dose of each drug into 'chlorpromazine equivalents' mg a day, and adding these together (where a cumulative dose of more than 1000 mg a day chlorpromazine equivalents is a 'high dose')
- by converting the dose of each drug into a percentage of the *BNF* maximum dose for that drug and adding these together (where a cumulative dose of more than 100% is a 'high dose').

Both of these methods have their limitations. Chlorpromazine equivalents are based on a combination of limited clinical evidence and the relative potency of antipsychotics in blocking dopamine D₂ receptors (Atkins *et al*, 1997). However the tolerability of an antipsychotic at high doses is likely to be dictated by side-effects that are not mediated through D₂ receptor blockade (for example, hypotension mediated via α -adrenergic antagonism or sedation mediated through H₁ antagonism). There is no universally accepted table of chlorpromazine equivalents; different sources give different equivalent doses. Psychiatrists' understanding of equivalent doses in clinical practice is often different again and there is no easy method for converting second-generation ('atypical') antipsychotic doses into chlorpromazine equivalents. In addition, a 'high dose' calculated by this method may bear little resemblance to the maximum dose contained in the summary of product characteristics.

The method that adds the percentage of the *BNF* maximum dose for each drug is simpler in that, trifluoperazine aside, there is a clearly stated *BNF* maximum dose for every antipsychotic drug. One problem with such an approach is that it takes no account of the use of combined drugs with contrasting mechanisms of action, which might be related both to therapeutic efficacy (such as augmenting clozapine with amisulpride or sulpiride, see

chapter on Treatment-resistant schizophrenia) or side-effects and tolerability. Further, some combinations of antipsychotic drugs are more potentially toxic than others. For example a prescription for flupentixol depot 400 mg/week and chlorpromazine 1000 mg/day would be 200% *BNF* maximum. A prescription for olanzapine 20 mg/day and haloperidol 30 mg/day (assuming the patient has a treatment-resistant illness) would also be 200%, but it is unlikely that these combinations would have an equivalent liability for side-effects. The Consensus Working Group agreed to take the following as a definition of high dose:

A total daily dose of a single antipsychotic which exceeds the upper limit stated in the summary of product characteristics or *BNF* and a total daily dose of two or more antipsychotics which exceeds the summary of product characteristics or *BNF* maximum using the percentage method.

The 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 may be minimised, alternative treatment strategies to high-dose prescribing and the use of audit to monitor practice.

Prevalence of high-dose regimens in clinical practice

IN-PATIENT STUDIES

The prevalence of high-dose prescribing has been most studied in psychiatric in-patients. Seven surveys, conducted in the UK over the past decade, involved a total of 4200 in-patients (Warner *et al*, 1995; Chaplin & McGuigan, 1996; Krasucki & McFarlane, 1996; Newton *et al*, 1997; Yorston & Pinney, 1997; Milton *et al*, 1998; Harrington *et al*, 2002a). About one-quarter of patients included in these studies were prescribed a high dose of antipsychotic medication. For the great majority of these, high dose was prescribed by virtue of polypharmacy; only 5% of those prescribed a high dose (about 1% of all in-patients) were prescribed a single antipsychotic at a dose above *BNF* limits.

The largest audit of prescribing for in-patients (Harrington *et al*, 2002a) provided a snapshot of the extent to which recommended best practice is followed. The results suggested poor adherence to monitoring recommendations. Many case notes failed to record the indications for, or outcome of, prescribing a high dose, or whether the patient was informed. In only 8% of patients had an ECG been carried out before the high-dose regimen was commenced.

The findings of a survey of 44 services (Harrington *et al*, 2002b) revealed great variation between mental health services in the proportion of in-patients who are prescribed a high dose; the figure ranged from 0 to 50%. Only a small proportion of this variation (26%) could be explained by simple differences in case mix, age, gender, ethnicity, diagnosis and status under the Mental Health Act. Compared with acute psychiatric wards, the prescribing of high doses appears to occur more frequently in psychiatric intensive care units (Cornwall *et al*, 1996; Hillam & Evans, 1996), rehabilitation wards and medium secure units (Lelliott *et al*, 2002), presumably because the patients are either more disturbed or have a mental illness that is more refractory.

INTERPRETATION OF THE FINDINGS

A number of issues should be borne in mind when considering these survey findings:

- The methods used are likely to overestimate the practice of high-dose prescribing for in-patients. This is because the surveys were mostly cross-sectional, recording prescribing practice on a single day. Thus, patients with longer lengths of stay, and therefore probably with

higher levels of disability and disturbance, will be over-represented in such surveys compared with longitudinal studies of consecutive admissions.

- The nature of the surveys also means that no conclusions can be made about long-term prescribing practices and, in particular, the proportion of patients discharged on a high dose. Little is known about how frequently patients receiving community care are prescribed high-dose antipsychotics.
- In clinical practice, antipsychotics are often prescribed on in-patient wards 'as required' (PRN), for use if patients are agitated or aggressive. In the largest survey of high-dose prescribing, about half of the patients fell into the category of high-dose prescribing only by virtue of PRN antipsychotic medication; much of this was not actually administered on the day of the survey (Harrington *et al*, 2002a). This confirmed the finding of Milton *et al* (1998) that prescriptions for PRN antipsychotics greatly increased the number of patients who might potentially be given higher than *BNF* doses of medication, although only 4–5% of PRN prescriptions were actually dispensed.
- The prevalence of high-dose prescribing might have changed because of the increasing use of second-generation antipsychotics. Even the most recent of the surveys was conducted in 1998, before the publication of the NICE Technology Appraisal Guidance on atypical antipsychotics and the NICE treatment guidelines for schizophrenia (National Institute for Clinical Excellence, 2002).

Factors influencing the use of high-dose antipsychotics

AGGRESSIVE BEHAVIOUR

There are suggestions from the literature that high-dose antipsychotics are more likely to be prescribed for patients who display aggressive behaviour and who are treated on forensic units (Krakowski *et al*, 1993; Peralta *et al*, 1994; Lelliott *et al*, 2002). This has led to suggestions that high-dose antipsychotic medication is sometimes used in clinical practice to try to control persistent aggression (see chapter on Persistent aggression). However, Tavernor *et al* (2000) compared patients on greater than 1400mg of chlorpromazine equivalents and those on less than 1000mg in a high secure hospital, matching the groups for age, sex, Mental Health Act classification and ward dependency level. They found, using factor analysis, that aggression did not predict those who were prescribed high doses. The Brief Psychiatric Rating Scale (BPRS; Lukoff *et al*, 1986) 'thinking disturbance' measure was a more useful predictor, suggesting that treatment resistance and chronicity may be more important factors.

ETHNICITY, GENDER AND AGE

In the largest UK survey of psychiatric in-patients prescribed antipsychotic drugs, 18% of 3576 were Black or from another ethnic minority group. The probability of a patient being prescribed a high dose was modelled using logistic regression. Independent variables included age, gender, ethnicity, Mental Health Act status and ward type. The patient variables that were found to increase the probability of being prescribed a high dose were younger age, male gender, a diagnosis of schizophrenia and being detained under the Mental Health Act. The effect of ethnicity was not significant.

We are not aware of any research that has examined the influence of patient variables on high doses of antipsychotics given for the purpose of rapid tranquillisation. However, one recent study of 1515 violent incidents on 14 general psychiatric wards over 3 years, found that Black patients were more likely to be given emergency medication (the dose was not specified) or secluded than White patients (Gudjonsson *et al*, 2004). However, after controlling for potential confounding factors, such as age, gender, the target of assault and the Mental Health Act 1983 status of the patient, the effect of the ethnic background of the patient was no longer significant (Gudjonsson *et al*, 2004).

Risks of high-dose antipsychotic drug use

DOSE-RELATED ADVERSE REACTIONS

It is self-evident that the risk and intensity of the majority of unwanted effects from antipsychotic drugs increase with dosage, but perhaps less well appreciated is the fact that risk also rises with the speed of drug delivery (American Psychiatric Association, 1997). However, some reactions are unpredictable in these terms and may reflect particular host susceptibilities, and have therefore been called idiosyncratic. For some types of unwanted effect, the character is neither clearly idiosyncratic nor dose-related. This chapter considers reactions that are either clearly dose-related or possibly dose-related. Appreciation of dose-response relationships is crucial for an informed assessment of the risk-benefit evaluation of antipsychotic agents, and this is especially true for the first-generation antipsychotic drugs which have potent actions on a wide range of receptors, and many of which were marketed before the establishment of the Committee on the Safety of Medicines. Their risks and benefits were therefore the subject of much less intense scrutiny and, despite the subsequent assessment by the Committee on the Review of Medicines, their licensed dose ranges tend to be relatively liberal and only loosely evidence-based. Certain members of the second-generation of antipsychotics (such as olanzapine and risperidone) have licensed dose ranges that are relatively narrow, which in itself may reduce the risk of serious adverse events within the permitted range.

PHARMACOLOGICAL CONSIDERATIONS

The key question with regard to the mechanisms of action of antipsychotic drugs is whether there is added value with respect to a drug's locus of action by elevating the dose above the registered therapeutic dose. This question is probably best answered by considering the dose-response relationships of antipsychotics at their receptor sites using the functional imaging techniques of positron emission tomography (PET) or single photon emission tomography (SPET). To date, the most validated mediators of anti-psychotic action remain the dopamine D₂ receptor and the 5-HT₂ receptor (Creese *et al*, 1976; Meltzer, 2003). The simple question is, therefore, whether additional dopamine or 5-HT₂ receptors are recruited at higher doses. The original work of Farde *et al* (1988, 1992) suggested that standard doses of a range of antipsychotics were associated with receptor blockade of greater than 70%. Even at standard doses, many antipsychotic drugs will produce greater levels of blockade than that, but the only consequence is to produce higher levels of extrapyramidal side-effects (EPS).

Pilowsky *et al* (1993) conducted an informative study in this field: a naturalistic survey of both treatment-responsive and treatment-resistant patients receiving a range of doses of antipsychotics. The investigators found that the dopamine receptors were fully saturated for all doses (high and low) and for both treatment-resistant and treatment-responsive schizophrenia and that there was no relationship between dopamine-binding indices and higher dosage (in terms of chlorpromazine equivalents, mg a day). This group has also performed some work on the limbic selectivity profiles of antipsychotic drugs. It has been argued that high-dose antipsychotics may selectively recruit limbic receptor systems. However, it is clear from these studies that a high level of saturation prevails for low and standard doses of drugs within limbic areas and the only consequence of raising the dose is to recruit more basal ganglia dopamine receptors (Pilowsky *et al*, 1997; Bigliani *et al*, 1999).

The dose-response relationship with 5-HT₂ receptors is even more clear-cut. It was apparent with very early studies that very low doses of second-generation antipsychotics could fully saturate 5-HT₂ receptors (Nyberg *et al*, 1993). This has been more systematically demonstrated with a range of antipsychotics (Travis *et al*, 1998). In addition, a comprehensive dose-response study by Nyberg *et al*, (1999) demonstrated that all 5-HT₂ systems were fully saturated at sub-therapeutic doses of second-generation antipsychotics. Therefore it is unlikely that any gain will be achieved from high-dose strategies via the 5-HT₂ receptor system.

There are more subtle neurochemical theories for the mechanism of action of antipsychotic drugs, such as a D₂/5-HT₂ balance theory and theories relating to the role of alpha, histaminergic and glutamatergic receptors (Meltzer, 2003). However, pharmacogenetic studies suggest that these receptors make a very weak contribution to the actions of antipsychotic drugs, making it unlikely that they contribute anything in high-dose strategies (Kerwin *et al*, 2003).

Another way of examining the pharmacology of high-dose strategies is to look at the clinical pharmacology of those second-generation drugs with relatively selective mechanisms of action. For instance, risperidone is a highly selective and highly potent D₂/5-HT₂ blocker (Nyberg *et al*, 1993) but a wide range of studies have clearly shown that higher doses of this drug are associated with a deteriorating therapeutic effect and a higher side-effect burden (Borison *et al*, 1992). Similarly, the drug sertindole also has a selective D₂/5-HT₂ profile. A large multi-dose study by Zimbroff *et al* (1997) showed relatively little difference between the higher and lower doses of the drug compared to multiple doses of haloperidol. The recently introduced drug aripiprazole has a mechanism of action characterised by a partial agonist effect at D₂ receptors. The striking thing about this agent is that it has a flat clinical dose-response curve with no difference between higher and lower doses (Kane *et al*, 2002b).

In conclusion, examination of the current pharmacological literature does not provide support for high-dose strategies on the basis of the mechanism of action of antipsychotics as we currently understand it. However, it is the experience of most clinicians that a small number of patients do well on combination and higher doses. These drugs have polyvalent receptor profiles, therefore it could be that there is a cryptic mechanism of action that is recruited at higher doses. It is also clearly the case that, at an individual level, patients may have genetically determined differences in response profiles that may justify a degree of dose finding in clinical practice (Bingefors *et al*, 2003).

POTENTIAL GENDER AND ETHNICITY FACTORS AND HIGH-DOSE STRATEGIES

Since it is now clear that there are well-defined gender and inter-ethnic variations in response to drugs, it is worth considering whether this is relevant to the definition of what constitutes a high dose in different sub-populations.

GENDER

With regard to the issue of gender, there are some general principles that need to be applied. From the first principles of pharmacokinetics it is clear that body build, weight and body mass index all conspire to affect the dose requirement of any therapeutic agent, including antipsychotics. Hormonal transitions also influence drug response (Seeman, 2004). These considerations alone would suggest that the threshold for determining what is a high dose for females should be scaled down, but there are no guidelines as to precisely by how much this should be. There are also important issues regarding pregnancy and childbearing potential that are pertinent to high-dose prescribing in females. This is an area that is relatively unstudied, but common sense would suggest that a more cautious approach should be taken with women. There is also the issue of whether there is a gender-specific propensity to hyperprolactinaemic side-effects. Again, there is little relevant research, but it would be prudent to consider these issues when considering dosing regimens.

Another relevant question is whether there is a lower requirement for antipsychotic drugs in females because the oestrogen status of premenopausal females confers a higher sensitivity to dopamine-blocking drugs. This has been reviewed by Salokangas (2004), where in a sample of 4338 patients with schizophrenia this author found that the daily doses of antipsychotic drugs required to sustain symptom control were higher in males than in females. Salokangas (2004) discussed in detail the oestrogen sensitisation hypothesis, but did not address simpler pharmacokinetic hypotheses, such as those described above.

The broad conclusion, however, is that females require lower doses of antipsychotic drugs than males in high-dose scenarios.

ETHNICITY

Ethnicity is a slightly more complex issue than gender. Some ethnic groups may have lower requirements for antipsychotic drugs. For example, Chinese patients seem to require lower doses of antipsychotics and have a higher response rate for clozapine in treatment-resistant schizophrenia than other ethnic groups, while Asian patients may have a lower dose threshold for a variety of extrapyramidal side-effects (Chiu *et al*, 2003; Chong *et al*, 2003; Liu *et al*, 2003).

Practitioners may be particularly concerned with whether higher doses are required for African and African-Caribbean patients. While there is evidence that such patients may be prescribed higher doses of antipsychotics and more often receive depot preparations and conventional antipsychotics than second-generation antipsychotics (Copeland *et al*, 2003, Kreyenbuhl *et al*, 2003), no research has addressed whether this is due to

an ethnopharmacological requirement for higher doses or related to more subtle sociocultural influences on prescribing patterns. Generally, the wide variability observed in individuals treated with psychotropic drugs suggests that therapeutic response is a complex trait influenced by several genes, and genetic polymorphisms at both the metabolic level and site of action are likely to contribute to the overall response to a particular drug (Kerwin & Arranz, 2004). Pharmacogenetics is the study of this variability and is more than 50 years old. Probably the most extensively studied polymorphisms are those of the cytochrome P450 system, which is responsible for the oxidation of a large range of drugs including many antipsychotics and antidepressants (King, 2000). Some polymorphisms of the CYP450 1A2 and 2D6 isoenzymes, which are involved in the metabolism of antipsychotics, give rise to 'poor metabolisers' who have higher blood levels of the unmetabolised parent drug for a given dose. There are ethnic differences in the distribution of such poor metabolisers such that, for example, there is a lower incidence of poor metabolisers in the Arab (1%), Asian (1%) and Black (3%) populations than in the White population (5–10%) for CYP450 2D6 (DeVane, 1998). Thus, the risk of high parent antipsychotic drug levels should, in fact, be lower in those ethnic minorities.

ADVERSE EFFECTS

The relationship between the extent of antagonist action at D₂ receptors and extrapyramidal side-effects has already been referred to above. It is safe to assume that any antipsychotic may lower the seizure threshold, and it has been suggested that antipsychotics with relatively potent antagonistic effects at histamine, serotonergic and noradrenergic receptors may be more liable to do this (McConnell *et al*, 1997). Barnes & McPhillips (1999) reviewed the unwanted effects of second-generation antipsychotics, and those which are dose-related within the licensed range include tachycardia, postural hypotension, sedation, seizures and, in some cases, hyperprolactinaemia. However, it must be emphasised that there is still a relative lack of robust data comparing the relative risk of these various adverse effects between the second-generation agents.

Hyperprolactinaemia is the result of antagonist action at D₂ receptors located on pituitary lactotrophs, and although roughly dose-related it can occur also at low doses (Wieck & Haddad, 2002). In addition to the well-documented effects of hyperprolactinaemia on sexual function, osteoporosis is a long-term and potentially disabling consequence of high prolactin (Ataya *et al*, 1988; Abraham *et al*, 2003; Halbreich *et al*, 2003). All antipsychotics appear prone to cause weight gain, with a spectrum of weight gain liability emerging with the second-generation drugs (Allison & Casey, 2001; Bobes *et al*, 2003; McIntyre *et al*, 2003). The mechanism for this is not entirely clear. It is often unrelated to dose, although it may be related to anti-serotonergic actions, and Reynolds *et al* (2002) have shown that a 5-HT_{2C} genetic polymorphism is implicated. There is ample epidemiological evidence that weight gain has highly undesirable consequences, quite apart from body image; the risks of obesity include type II diabetes, hypertension and coronary heart disease, all of which incur morbidity and reduced life expectancy (American Diabetes Association *et al*, 2004).

Sedation is more clearly dose-related, and thought to reflect blockade at central histamine and/or α_1 -noradrenergic receptors. Some troublesome

peripheral autonomic effects, such as dry mouth, constipation and urine retention, are related to atropinic actions, and antipsychotics with relatively high intrinsic anticholinergic action, such as thioridazine and clozapine, might be expected to generate more of these problems (Chengappa *et al*, 2000). Clozapine may cause paradoxical hypersalivation through a complicated action at cholinergic receptors on salivary glands (Davydov & Botts, 2000). Neuroleptic malignant syndrome appears to be related to D₂ blockade, it is loosely dose-related, and the risk is higher with rapid increases in dose and with intramuscular administration (Keck *et al*, 1989; Viejó *et al*, 2003). The thankfully rare, but serious, reaction of retinitis pigmentosa is particularly associated with thioridazine at daily dose levels in excess of 600mg. All of these potential adverse effects need to be balanced against the significant potential health gain of receiving effective treatment.

CLINICAL IMPLICATIONS

- Our current state of knowledge does not allow for any plausible pharmacological rationale for high-dose antipsychotic medication.
- High-dose regimens are associated with a greater risk of adverse effects.

Cardiac side-effects of antipsychotics: relationship to dose

A link between antipsychotics and ventricular tachycardia and sudden death was made soon after their use in clinical care became widespread, but in the intervening four decades no consensus has been achieved on the frequency of these events, or even whether a true causal association exists (Royal College of Psychiatrists, 1997). There is therefore a dilemma of balancing the unknown risks of rare but serious adverse reactions against the undoubted benefits of long-term treatment.

Electrocardiogram abnormalities indicating abnormal repolarisation are present in significant proportions of patients on antipsychotics (Hollander & Cain, 1971). The conventional measure of ventricular repolarisation is the QT interval: the time from the onset of ventricular depolarisation to completion of repolarisation. The QT interval is subject to a number of influences, including gender, age, time of day and heart rate. The effect of heart rate has led to the widespread adoption of the QTc (QT interval with a correction for heart rate) as a more appropriate measure. However, there are problems in reliability of the measurement of QT and there is only weak consensus on the cut-off points for abnormality (Moss, 1993). Furthermore, interpretation of case reports of arrhythmia and sudden death in patients receiving these drugs is complicated because psychiatric patients are known to be at a high risk of cardiovascular death (Ruschena *et al*, 1998) as they have a high prevalence of risk factors for cardiovascular disease (Royal College of Psychiatrists, 1997).

RISK FACTORS FOR QT_c PROLONGATION AND ASSOCIATED ARRHYTHMIAS

QT interval prolongation may be congenital or acquired. Congenital long QT syndromes are rare, and result from mutations of genes that code for specific components of cardiac ion channels. Prolongation of the QT interval may place the individual at an increased risk of cardiac arrhythmias, particularly the characteristic polymorphic ventricular tachycardia termed 'torsade de pointes'. Patients who have abnormal ventricular repolarisation are at increased risk of developing arrhythmia when started on drugs that prolong repolarisation further. Indicators of abnormal repolarisation include abnormalities of the T-wave or large U-waves, as well as QT prolongation. Patients who have had previous episodes of torsade de pointes are at particular risk, even if a different drug had provoked it. Patients with pre-existing cardiac disease such as left ventricular dysfunction or hypertrophy are also at increased risk. Age may be an independent risk factor. Torsade

de pointes is most likely to occur when the heart rate is slow and in the presence of extrasystoles. Thus, conditions associated with these factors, such as heart block, increase the risk of torsade. The arrhythmia is more likely to occur in the presence of electrolyte abnormalities, for example hypokalaemia, hypocalcaemia or hypomagnesaemia. Treatment with diuretics also appears to increase the risk, probably by producing such electrolyte abnormalities. Patients with alcohol dependence may be at increased risk because of associated liver disease, which increases the risk of QTc prolongation and sudden death (Day *et al*, 1993). Women have a longer QT interval on average than men (Rautaharju *et al*, 1992) and epidemiological studies have consistently shown that a disproportionate number of episodes of drug-induced torsade de pointes occur in women (Makkar *et al*, 1993).

ANTIPSYCHOTICS AND THE RISK OF ARRHYTHMIA AND SUDDEN DEATH

Some antipsychotic drugs are more potent than others at producing QT interval prolongation and arrhythmias at therapeutic doses. This depends on their relative potency for producing their clinically intended effect compared with their potency at provoking prolongation of the QT interval. The most important mechanism of action is mediated by blockade of the delayed rectifier potassium channel, I_{Kr} . This prevents the outward movement of potassium that is responsible for ventricular repolarisation. As far as antipsychotics are concerned, this is an entirely separate mechanism from their primary pharmacological action and therefore a risk of arrhythmia is entailed which is not associated with any clinical advantage. There is evidence that torsade de pointes most often occurs disproportionately early during therapy, which has implications for monitoring since it would be logical to focus this at the time of highest risk.

Initially there were case reports and case series of arrhythmias and sudden, unexpected deaths with antipsychotics that highlighted the risk of higher doses. Reports of 13 sudden deaths in recipients of pimozide prompted the UK Committee on Safety of Medicines (1990) to issue specific recommendations on the use of this drug which include gradual dose escalation and the recording of an ECG before and periodically during treatment in those receiving high doses. Haloperidol exhibits no clear effect on QTc at low or at moderate daily doses but has been associated with cases of QTc prolongation and torsade de pointes at higher doses (above 20 mg a day) and in overdose. High-dose intravenous haloperidol seems particularly likely to prolong QTc, and sudden death has also been reported in patients taking haloperidol. These risks are higher in patients who are medically ill (Lawrence & Nasraway, 1997). Intravenous droperidol has also been shown to induce a dose-dependent prolongation of QTc (Lischke *et al*, 1994). A disproportionate number of case reports of arrhythmia and sudden death involved thioridazine. Doses of 100mg daily or more caused QT interval abnormalities in over half of recipients (Buckley *et al*, 1995a). Thioridazine-induced QT prolongation has been linked to plasma concentration (Hartigan-Go *et al*, 1996). A study in Finland of 49 cases of sudden death affecting patients taking psychiatric drugs found that 46 were exposed to a phenothiazine and in 28 cases this was thioridazine. This figure was out of proportion to the local use of the drug (Mehtonen *et al*, 1991).

Controlled data are now emerging which have elucidated the nature of the association between antipsychotics and arrhythmias and are more definitive on the effect of high dose. There is ample evidence that QT prolongation and resulting arrhythmias are concentration-related effects in animals (Drici *et al*, 1998). Warner *et al* (1996) showed that QTc prolongation (defined as >420ms) was more common in the treated patients than in controls, particularly in those taking high doses (more than 2000mg chlorpromazine equivalents a day). Reilly *et al* (2000) found that predictors for prolonged QTc were being over 65 years of age, receiving tricyclic antidepressants, and the use of either thioridazine or droperidol. For antipsychotic drugs as a whole, the risk of QT prolongation was significantly greater if high (over 1000mg chlorpromazine equivalents) or very high (over 2000mg chlorpromazine equivalents) doses were used, compared to lower doses.

Epidemiological studies have identified risks for cardiac death related to antipsychotic use and have indicated the important role of high dose in this effect. Waddington and co-workers (1998) have linked antipsychotic polypharmacy with excess mortality in schizophrenia. Ray and colleagues (2001) investigated the rates of sudden cardiac death in Tennessee Medicaid enrollees and found that there were 11.3 deaths per 104 person years of follow-up in the unexposed group. This figure increased to 14.4 and 26.9 per 104 person years for current users of low and high doses of antipsychotics respectively. Multivariate-adjusted risk of death was increased 2.4 times in recipients of antipsychotic drugs. The risk was highest with thiothixene (relative risk (RR)=4.23, 95% CI 2.00–8.91), chlorpromazine (RR=3.64; 95% CI 1.36–9.74), thioridazine (RR=3.19; 95% CI 1.32–7.68) and haloperidol (RR=1.90; 95% CI 1.10–3.30). Reilly *et al* (2002) conducted a retrospective review of sudden deaths occurring in 5 psychiatric hospitals over a 12-year period. Most of the deaths were of elderly patients (median age of 69 years), most of whom had been in hospital for more than a year. Factors associated with sudden death included the presence of an organic psychiatric disorder, the presence of hypertension or previous myocardial infarction and treatment with thioridazine.

The above studies raised serious concerns about the safety of thioridazine, and resulted in regulatory changes, which restricted the indications for thioridazine in both the UK and USA. The manufacturers of droperidol have suspended marketing of this product. (Note: thiothixene has never been licensed in the UK.)

The epidemiological studies described above were all conducted before the widespread introduction of second-generation antipsychotic drugs, and provide no evidence about their relative safety. Summaries of the available open human volunteer and patient studies on second-generation drugs are given in a review by Taylor (2003). There appear to be only small effects at low doses, but at higher doses there are modest effects on QTc for the majority of such antipsychotics. This effect is better established for clozapine. The second-generation antipsychotic sertindole was linked with QT interval prolongation with 36 suspected fatal adverse drug reactions and 13 episodes of serious but non-fatal arrhythmia reported (Committee on Safety of Medicines, 1999). The manufacturers withdrew the drug in 1998. However, restrictions in the European Union were lifted in June 2002 following the receipt of further epidemiological and *in vitro* data. The risk of sudden death with second-generation antipsychotics is unknown but probably low. A case-control study is currently underway in the UK which may provide more systematic information (Appleby *et al*, 2000).

ADDITIONAL RISK FACTORS

GENETIC VARIATION IN METABOLISM

There are genetic polymorphisms for some hepatic enzymes responsible for the metabolism of drugs that cause QT prolongation and torsade de pointes. As a result, some patients who do not express individual isoforms may experience enhanced (parent drug causes QT prolongation) or attenuated (metabolite causes QT prolongation) ECG effects. Several antipsychotic (for example, thioridazine) and antidepressant drugs are hydroxylated via CYP2D6 (debrisoquine hydroxylase). Slow hydroxylators of debrisoquine achieve higher plasma concentrations of the parent drug and its metabolite than rapid hydroxylators (von Bahr *et al*, 1991).

DRUG INTERACTIONS

Pharmacokinetic drug interactions resulting in increased plasma or tissue concentrations of a QT interval-prolonging drug are a particularly important source of torsade de pointes. The most common interaction is via inhibition of the hepatic cytochrome P450 isoform CYP3A4. This isoform is important because it is very abundant in the human liver and is primarily responsible for the metabolism of many QT-prolonging drugs. The most important pharmacodynamic interaction is from the combined use of two drugs that prolong ventricular repolarisation, since these may have an additive effect on QT interval. It is important to note that some hepatic enzyme inhibitors (for example, erythromycin and ketoconazole) also delay cardiac repolarisation and this effect increases the severity of the interaction. In the context of antipsychotic drug therapy, there is increasing evidence of significant interaction with selective serotonin reuptake inhibitors and tricyclic antidepressants. Interaction with the latter is of particular importance since these drugs also produce QT prolongation independently. A more detailed account of important interactions between psychotropics with potential for alterations of the QTc can be found in the review by Taylor (2003).

SETTING

Several of the case reports of sudden death involve agitated patients undergoing restraint (Jusic & Lader, 1994; Lareya, 1995). Concerns have been raised that patients may be at increased risk of arrhythmia during such physiological activation as a result of increased sympathetic activity. To date, epidemiological studies suggest that this association is uncommon (Reilly *et al*, 2002).

DRUGS OF ABUSE

The impact of recreational substances on cardiac repolarisation and sudden cardiac death is unclear (Royal College of Psychiatrists, 1997). QT interval prolongation has been reported with ecstasy, cocaine and methadone (Drake & Broadhurst, 1996, Perera *et al*, 1997) and sympathomimetic agents may increase the risk of ventricular arrhythmias independent of any effects on repolarisation. However, there are few published data in this area and further research is needed.

CLINICAL IMPLICATIONS

- Attention should be paid to the general health of patients with psychosis. Modifiable risk factors for ischaemic heart disease (including smoking, hypertension, hyperlipidaemia, sedentary lifestyle and obesity) should be identified and managed appropriately.
- The use of antipsychotic drugs with more pronounced effects on cardiac repolarisation can only be justified if the drug has specific advantages for the patient in comparison to antipsychotic drugs with less marked cardiac risks. High doses and drug combinations should only be used when there is a clinical justification, particularly if the combination may result in a drug interaction or additive ECG effects.
- All patients should be assessed for cardiovascular disease prior to the institution of antipsychotic drug therapy, regardless of dose. This should, whenever possible, include an ECG, which should be examined for evidence of ischaemic heart disease, left ventricular hypertrophy and repolarisation abnormalities. The presence of such factors may affect the choice of antipsychotic drug or increase the frequency of monitoring required, as well as prompt a more detailed cardiac assessment.
- An ECG prior to, and ECG monitoring during, antipsychotic therapy is particularly important in the following situations where:
 - higher risk antipsychotic drug treatment is contemplated (for example, pimozide and haloperidol. Special precautions pertain for sertindole, and these are embodied in the summary of product characteristics)
 - high-dose or parenteral antipsychotic drug therapy is to be used
 - the patient receiving the medication has a history of cardiovascular disease. Urea and electrolytes should also be checked, particularly plasma potassium, especially in patients at higher risk of electrolyte abnormalities, due, for example, to anorexia nervosa, diuretic use or dehydration. ECGs should be performed every few days following initiation of such therapy or during a period of dose escalation, until it is judged that steady state concentrations have been reached. Thereafter, ECG and electrolyte assessment is recommended every few months, at times of acute illness, when potentially interacting drugs are introduced or if the patient experiences symptoms that could be due to arrhythmia, for example syncope or fits (Yap & Camm, 2000).
- Under the circumstances of rapid tranquillisation where assessment of cardiovascular disease and status is difficult and ECGs impossible, it is prudent to avoid high doses of antipsychotics, particularly parenterally.

Acute violence and emergency tranquillisation

DEFINITION

Rapid tranquillisation can be defined as the use of psychotropic medication to control agitated, threatening or destructive behaviour (Ellison *et al*, 1989). In clinical practice, dosages exceeding *BNF* recommended limits are commonly used for rapid tranquillisation (Cunnane, 1994; Simpson & Anderson, 1996; Mannion *et al*, 1997). Only a limited amount of clinical research data exists regarding the use of high-dose medication in rapid tranquillisation. Further, there appears to have been a lack of consensus regarding medication choice in rapid tranquillisation, which has been confounded by the changes in aims of rapid tranquillisation over recent years (Cunnane, 1994; Battaglia, 2005).

PHARMACOTHERAPEUTIC PRACTICE

The choice of pharmacotherapy in acute/emergency situations should take account of the fact that with antipsychotic medication a rapid antipsychotic therapeutic effect (as opposed to sedation) is not possible: this will take several days or even weeks (Agid *et al*, 2003), regardless of which drug or doses are used.

The working group would endorse the latest guidance on good practice in rapid tranquillisation and management of acute violence, which may be found in a number of documents produced by the Royal College of Psychiatrists (for example, Royal College of Psychiatrists Research Unit, 1998) and by the National Institute for Clinical Excellence (National Collaborating Centre for Mental Health, 2002; National Collaborating Centre for Nursing and Supportive Care, 2005).

CLINICAL IMPLICATIONS

- Clear policies for rapid tranquillisation should be agreed locally, identifying specific drugs, doses and routes of administration, together with type and frequency of monitoring following administration. These should be consistent with current national guidelines.
- The use of high-dose antipsychotic medication for rapid tranquillisation is an exceptional practice, and should only be considered when other pharmacological and non-pharmacological strategies have not been successful.

Acute psychotic episodes and switching medication

PHARMACOLOGICAL RATIONALE

It is important to understand that antipsychotic action does not in itself include sedation and that this is essentially an unintended effect, mediated by non-target anti-histaminergic or anti-adrenergic actions of an individual drug, rather than by its key anti-dopaminergic action. In acute treatment, to employ an antipsychotic drug to induce sedation is actually to prescribe a drug for its side-effects. These effects are less predictable, varying between drugs and between patients, and will appear at a different, usually a higher, dose than the antipsychotic effects, so increasing the likelihood of high-dose prescribing.

EVIDENCE FOR EFFICACY

The aims of drug treatment in the acute episode are best articulated in a treatment plan. Typically, this would have as its aims:

- the improvement of psychotic symptoms
- the improvement of ancillary symptoms such as agitated or disturbed behaviour; affective features such as anxiety; disturbed sleep
- treatment of possible emergency situations, with behavioural disturbance (see chapter on Acute violence and emergency tranquillisation)
- minimising and managing adverse effects
- maintaining future remission.

In the past, clinicians would not uncommonly adopt a strategy of 'rapid neuroleptisation' when treating an acute psychotic relapse. High loading doses were used to produce remission more rapidly and effectively. While early, open studies exploring this approach were encouraging, subsequent controlled studies comparing rapid neuroleptisation and standard dosage regimens found no superiority for the former in either degree or rapidity of response (Kane, 1993). Overall, such attempts to achieve immediate high steady-state plasma levels have been shown to be unsafe and unnecessary (King, 1994).

The Working Group endorses the good practice recommendations for the treatment of acute psychotic episodes provided in guidelines published by NICE (2002) and the Royal College of Psychiatrists (1997).

SWITCHING MEDICATION

Changing over from one antipsychotic drug to another will involve a period of polypharmacy while the drug treatments overlap, with the potential for high combined dosage. The best way of switching from one drug to another, in order to minimise adverse effects, including discontinuation symptoms, has not been well examined empirically. One randomised trial comparing methods of switching from a conventional drug to olanzapine found that the optimal strategy was to overlap the two drugs, commencing the new drug at its usual starting dose before tapering off the previous drug (Kinon *et al*, 2000).

CLINICAL IMPLICATIONS

- The local implementation of current national guidelines (see above) should include clear protocols for the management and treatment of acute psychotic episodes. Adherence to such protocols should minimise the use of high-dose antipsychotic medication.
- Initiation of antipsychotic drug treatment in the first episode or in a subsequent untreated episode after a drug-free period should never involve starting more than one drug at the same time.
- Obtaining a second medical opinion should be considered when standard approaches to acute treatment have failed.

Persistent aggression

PHARMACOLOGICAL RATIONALE

There is no research evidence in the literature examining whether antipsychotic medication prescribed at higher than *BNF* limits is effective in the management of persistent aggression associated with psychosis, or more effective than antipsychotics prescribed within *BNF* limits. Where high-dose antipsychotics have been used in persistently aggressive psychotic patients it is often unclear whether the rationale for dose escalation is an attempt to get a better response to the antipsychotic action or to increase the associated sedation.

EVIDENCE FOR EFFICACY

Until recently, first-generation antipsychotics were used to treat patients with persistent aggression associated with psychosis, as well as agitation and aggression in a broader range of medical settings (Buckley, 1999). However, it is unclear whether such antipsychotics selectively target aggression independent of their antipsychotic and sedative effects. There is a serious paucity of research examining the effectiveness of first-generation antipsychotics in normal or high doses in controlling persistent aggression. McEvoy *et al* (1991) compared the response of patients to haloperidol in a mean dose of 3.4 mg daily with that of those given a mean dose of 11.6 mg daily (both within recommended *BNF* limits). They found that the higher dose of haloperidol did not lead to greater improvement in measures of psychosis but did produce a slightly greater decline in measures of hostility. The group receiving the higher dose suffered from considerably more, distressing extrapyramidal side-effects.

Akathisia has been found to be a risk factor for violence (Van Putten, 1975; Keckich, 1978; Raja *et al*, 1997) and therefore high doses of antipsychotics might increase the risk of aggression because of the greater risk of akathisia. It is important to note that dysphoria may be the first and sometimes only sign of the dysphoria/akathisia syndrome (King *et al*, 1995) and may therefore be associated with a higher risk of aggression. However, a study comparing aggressive and non-aggressive patients with schizophrenia found no statistical difference in the level of akathisia (Cheung *et al*, 1996).

There is emerging evidence that some second-generation antipsychotics, especially clozapine, used within *BNF* limits, may reduce persistent aggression in schizophrenia (for detailed reviews see Glazer & Dickson, 1998; Buckley, 1999; Volavka & Citrome, 1999). Studies have tested

clozapine (Garmendia *et al*, 1991; Volavka *et al*, 1993; Buckley *et al*, 1995b; Menditto *et al*, 1996; Rabinowitz *et al*, 1996), risperidone (Czobor *et al*, 1995; Buckley *et al*, 1997; Marder *et al*, 1997) and olanzapine (Beasley *et al*, 1998) in this regard. Some studies of second-generation drugs in the management of aggression have had methodological flaws (see Volavka & Citrome, 1999); for example, not all have control groups; they differ in their definition of aggression; some use very indirect measures of aggression such as the Brief Psychiatric Rating Scale (BPRS; Lukoff *et al*, 1986) or Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987) hostility scale; most are open-label; the frequency of aggressive incidents is generally low; and there may be recruitment bias. Further randomised controlled trials specifically looking at aggression and violence are needed.

CLINICAL IMPLICATIONS

- There would appear not to be any justification from the published literature for the use of high-dose antipsychotic medication for the treatment of persistent aggression in schizophrenia
- The clinical management of persistent aggression in schizophrenia should involve:
 - thorough assessment of the patient
 - use of the best available evidence to treat the psychotic symptoms as effectively as possible
 - regular review of the use of PRN medication, and the supervision of junior staff prescribing it
 - initiation of appropriate clinical interventions for other disorders, for example, substance misuse and personality disorder
 - consideration of clozapine for patients who are resistant to treatment and are persistently aggressive
 - consideration of other management techniques such as: improving adherence with medication; de-escalation and psychological techniques; in-patient ward layout, size, patient mix and environment; minimising extrapyramidal side-effects; and use of close observations in the acute situation
 - ensuring that staff are well trained in the management of aggression, and adhere to the principles in the guidelines referred to in the section on Pharmaceutical practice in the chapter on Acute violence and emergency tranquillisation above.

Relapse prevention

PHARMACOLOGICAL RATIONALE

Many attempts have been made to demonstrate a dose–response relationship for antipsychotics using plasma levels. During the 1970s and 1980s very high doses were employed, but this literature produced no consistent or robust findings (King, 1994). In fact the ‘neuroleptic threshold’, the dose at which the first signs of extrapyramidal side-effects occur, is similar in patients and healthy volunteers (about 4 mg haloperidol), and the majority of patients respond to low/modest doses of haloperidol (5–10 mg/day; the *BNF* maximum recommended dose now being 30 mg/day). It is the drug concentration in the brain rather than the dose or plasma drug level that is important. With the advent of PET and SPET neuroimaging it is now possible to monitor this *in vivo* in both patients and healthy volunteers, and techniques have become increasingly more sophisticated with the introduction of new radioligands (Talbot & Laruelle, 2002).

EVIDENCE FOR EFFICACY

Studies of relapse prevention have tended not to study high-dose regimens, but rather have compared low-dose and intermittent, targeted treatment strategies with standard-dosage regimes. Nevertheless, such studies have provided relatively consistent and robust evidence that, for conventional antipsychotics, the recommended dose ranges are optimal for relapse prevention in psychotic illness, principally schizophrenia (Kane *et al*, 2002a; Marder & Wirshing, 2003). The guideline from the schizophrenia patient outcomes research team (PORT) recommends a maintenance dosage of 300–600 mg chlorpromazine equivalents daily, partly on the basis that no advantage has been demonstrated for doses above 600 mg chlorpromazine equivalents (Lehman *et al*, 1998a,b).

Compared to oral antipsychotics, depot preparations increase the risk of excess dosage (Walkup *et al*, 2000), an issue noted in the NICE schizophrenia treatment guidelines (National Institute for Clinical Excellence, 2002). Addressing the issue of depot medication pharmacotherapy for relapse prevention, these evidence-based guidelines stated that ‘For optimum effectiveness in preventing relapse, depot preparations should be prescribed within the standard recommended dosage and interval range’.

CLINICAL IMPLICATIONS

- There would appear not to be any justification from the published literature for the use of high-dose antipsychotic medication for relapse prevention in schizophrenia.
- If patients with schizophrenia suffer an exacerbation of psychotic symptoms despite receiving maintenance antipsychotic medication in standard recommended dosage, it is not uncommon for the dose of medication to be increased to try to treat the episode. However, there is no convincing evidence base to support the continuation of the consequent higher dose of antipsychotic medication long term or the prescription of further dose increments with subsequent episodes of psychotic relapse.

Treatment-resistant schizophrenia

PHARMACOLOGICAL RATIONALE

It has been estimated that between one-fifth and one-third of patients with schizophrenia have a poor response to treatment despite an adequate trial of medication, and broadening the definition beyond symptoms to include vocational, social and cognitive domains would lead to an even higher proportion being classified as treatment-resistant (Barnes *et al*, 2003). When assessing the reasons for apparent non-response, it is important to exclude poor adherence to medication and covert co-morbid substance use.

Attempts to find either a pharmacokinetic or pharmacodynamic basis for treatment resistance have not been successful. Efforts to find a biological basis using either structural and functional neuroimaging (Lawrie *et al*, 1995) or eye movement investigations (Thampi *et al*, 2003) have been equally unrewarding. An intriguing possibility arises out of the findings of a key receptor occupancy study by Abi-Dargham *et al* (2000). They measured D₂ receptor binding potential before and after dopamine depletion by α -methyl-para-tyrosine in 18 untreated schizophrenic patients. A larger increase in D₂ receptor availability (a measure of synaptic dopamine) was found in these patients compared to controls. Furthermore, elevated synaptic dopamine predicted good treatment response of positive symptoms to antipsychotic drugs. A subgroup of patients showed no detectable abnormality of striatal dopamine function, despite frank psychotic symptoms, and failed to respond to treatment. These findings have led to the concept of dopaminergic- versus non-dopaminergic-driven psychotic states in schizophrenia. Thus, when faced with a persistent negligible response to antipsychotic medication (with either conventional or one of the second-generation antipsychotics) the evidence is that it would be more prudent to move to clozapine, as recommended by the recent NICE guidelines (National Institute for Clinical Excellence, 2002), rather than to try high-dose regimens.

Combined antipsychotics are commonly administered to tackle treatment-resistant psychotic illness, but contrary to past discredited theory, such a strategy is always associated with more rather than fewer adverse drug reactions. These may be inadvertent consequences of drug-drug interactions, particularly with SSRI antidepressants, most of which can cause clinically significant increases in antipsychotic plasma levels (see King, 2000; and Table 1). Such problems may be avoided by always consulting a desk reference or a physician's manual (such as the *BNF*) before an unfamiliar drug combination is prescribed. The use of more than one antipsychotic drug at a time is rarely justified but may occur when treating patients who relapse while receiving maintenance depot medication, or attempting to maximise the response in clozapine-resistant patients.

Table 1 Antipsychotic drug–drug interactions

<i>Pharmacodynamic</i>		<i>Pharmacokinetic</i>	
<i>Drugs potentiated</i>	<i>Drugs inhibited</i>	<i>Increased antipsychotic blood levels</i>	<i>Decreased antipsychotic blood levels</i>
<i>Central nervous system</i> ■ Alcohol ■ Benzodiazepines ■ Antihistamines ■ Anticholinergics ■ Opiates ■ General anaesthesia ■ Lithium	<i>Central nervous system</i> ■ Antiparkinson drugs ■ Anti-epileptic drugs	<i>Enzyme competitors</i> ■ Cimetidine ■ selective serotonin reuptake inhibitors <i>Propranolol</i>	<i>Enzyme inducers</i> ■ Carbamazepine ■ Phenytoin <i>Anticholinergics</i> <i>Antacids</i>
<i>Cardiovascular system</i> ■ Tricyclic antidepressants ¹ (arrhythmias) ■ Angiotensin converting enzyme inhibitors (hypotension)	<i>Cardiovascular system</i> ■ Digoxin ■ Adrenergic neurone blockers		

(Note: Always consult the latest edition of *British National Formulary*). ¹ Also elevated blood levels.

EVIDENCE FOR EFFICACY

HIGH-DOSE TREATMENT

In clinical practice, there may be a tendency for antipsychotic drug dosage to increase over time in those patients whose symptoms remain unresponsive to standard dosages, particularly when disturbed, aggressive behaviour is present. Over time, a patient may end up maintained on a high dosage although it may be difficult, in retrospect, to determine whether such a regimen has been associated with any benefit. More systematic testing of a high-dose regimen in patients with refractory illness, using an individual, time-limited trial, has been recommended (Hirsch & Barnes, 1994). But the results of the published trials in this area provide little support for a high-dose strategy. Only a few controlled studies comparing very high or 'mega' doses of conventional antipsychotics with standard-dosage regimens in treatment-resistant patients have been conducted, mostly in the 1970s. None of them demonstrated any therapeutic superiority for the high-dose regimen (Hirsch & Barnes, 1994; Thompson, 1994), and these studies had methodological flaws, such as small sample sizes, and the lack of a consistent, valid definition of treatment-resistance (Kane, 1993).

COMBINED ANTIPSYCHOTICS

As mentioned above, antipsychotic drugs are commonly prescribed in combination for those with a psychotic illness who have shown a lack of a satisfactory response to a single antipsychotic. Specifically, the addition of a

conventional antipsychotic to clozapine treatment would seem to be a relatively common strategy. In some European countries, conventional antipsychotics are added in approximately a third of patients receiving clozapine (Leppig *et al*, 1989; Peacock & Gerlach, 1994; McCarthy & Terkelsen, 1995).

The published evidence for the efficacy of combined antipsychotics in treatment-resistant schizophrenia is limited (Kontaxakis *et al*, 2005). For example, Yuzda (2000) only managed to identify two open prospective trials (Henderson & Goff, 1996; Mowerman & Siris, 1996), one retrospective review (Friedman *et al*, 1997), four anecdotal reports (McCarthy & Terkelsen, 1995; Gupta *et al*, 1998; Takhar 1999; Waring *et al*, 1999) and one randomised, controlled trial (Shiloh *et al*, 1997a). The majority of relevant case reports, case series and small studies deal with the addition of a conventional antipsychotic to clozapine monotherapy. The adjunctive antipsychotics tested include conventional agents such as pimozide (Friedman *et al*, 1997) and sulpiride (Shiloh *et al*, 1997b), and second-generation drugs such as olanzapine (Gupta *et al*, 1998), amisulpride (Kampf *et al*, 2005) and risperidone (Koreen *et al*, 1995; McCarthy & Terkelsen, 1995; Tyson *et al*, 1995; Chong *et al*, 1996; Henderson & Goff, 1996; Morera *et al*, 1999; Raskin *et al*, 2000; Adesanya & Pantelis, 2001).

More recent randomised controlled trials testing risperidone augmentation of clozapine in treatment-resistant schizophrenia (Josiassen *et al*, 2005; Yagcioglu *et al*, 2005; Honer *et al*, 2006) have yielded equivocal findings. Chong & Remington (2000) concluded that a limitation common to all the published studies in this area was the lack of data regarding the previous exposure of those participating in the studies to the adjunctive antipsychotic. They pointed out that in the absence of this information, it remained uncertain whether any clinical benefit that might follow the addition of a second antipsychotic should be attributed to the combination or simply to the second antipsychotic alone. Further, the combination of antipsychotics is not without hazard. Several investigators have questioned the safety of such combinations, and reported a range of adverse effects (Koreen *et al*, 1995; Godlesky & Sernyak, 1996; Raskin *et al*, 2000; Mujica & Weiden, 2001).

CLINICAL IMPLICATIONS

- The results of the published trials of high-dose antipsychotic medication for treatment-resistant schizophrenia provide no convincing evidence of efficacy.
- Overall, the efficacy of combining two or more first-generation antipsychotics or adding a first-generation antipsychotic to a second-generation drug (or vice versa) has not been established, and there is evidence for an increased risk of adverse effects and pharmacokinetic interactions.
- The NICE guidelines on core interventions in the treatment and management of schizophrenia (National Collaborating Centre for Mental Health, 2002) concluded that there was a consensus level of evidence that antipsychotic drugs, first or second generation, should not be prescribed concurrently, except for short periods to cover changeover. However, the addition of a second antipsychotic to clozapine may be considered for people with treatment-resistant schizophrenia for whom clozapine alone has proved insufficiently effective.

Responsibilities for prescribing, administering and dispensing

PHARMACY ISSUES, OFF-LICENCE PRESCRIBING AND LEGAL ISSUES

The use of high doses of antipsychotic medication raises issues of liability should the patient be harmed by the use of the medicine. The use of a medicine at doses that exceed the product's marketing authorisation is commonly termed unlicensed or off-label (see chapter on Definition of high dose under Antipsychotic monotherapy). The term 'unlicensed medicine' normally applies to those medicines that do not have a marketing authorisation (formerly referred to as a product licence), issued by the Medicines and Healthcare products Regulatory Agency (MHRA). However, it is also applicable to licensed medicines when they are used outwith the terms of the marketing authorisation. This includes the use of licensed medication at doses that exceed those defined in the marketing authorisation.

On its introduction in 1968, the Medicines Act laid down regulations to control the manufacture, sale and use of medicinal products. As discussed previously, medicines are required to have a marketing authorisation, issued by the Medicines and Healthcare products Regulatory Agency. This will include validation of the manufacture, storage and shelf life of the product together with its therapeutic benefit and adverse event profile. This is meant to assure the safety, quality and efficacy of a product throughout the life of that product. The marketing authorisation also defines the therapeutic purposes or indications for which a product may be sold or supplied. If a prescriber uses a licensed medicine outwith the terms of its marketing authorisation, then the manufacturer is unlikely to be held liable for any harm caused by that medicine, unless the harm is directly attributable to a defect in the medicine, rather than the way in which it was used.

Thus, whenever a medicine is prescribed outwith the terms of its licence (such as exceeding the recommended maximum dose), the prescriber is professionally accountable and liable for any harm caused. The liability situation for pharmacists and nurses is more complex. Pharmacists have a duty to ensure that each prescription that they dispense is assessed, to ensure that it is suitable for the individual patient. In hospitals, the pharmacist usually checks each prescription for suitability even if the medicine is available as a ward stock. Pharmacists should bring to the attention of the prescriber the fact that a medicine is being used outside the limits stated in the marketing authorisation.

The nurse would similarly need to assure him- or herself of the safety of the prescription before administering a medicine. Although it has not been tested by case law, it is likely that there would be shared liability between

the prescriber, the pharmacist and the nurse administering the medicine, although the bulk of the liability would rest with the prescriber.

A Hospital Trust is required to indemnify its employees against the financial consequences of personal liability claims in accordance with the Clinical Negligence Funding Scheme or equivalent, except where such negligence arises from the actions of bad faith, misconduct or gross lack of care. An employer cannot indemnify its employees against the personal consequences of criminal liability.

It is good practice to ensure that patients are aware of the fact that they are receiving a medicine at a dose outside of the marketing authorisation and the possible consequences of this. Quite apart from the ethical and moral reasons, this is sensible practice because most licensed medicines are dispensed in standard packages together with a patient information leaflet. This will state the recommended doses and may caution against exceeding the recommended doses or state a maximum dose.

SUPPLEMENTARY PRESCRIBING FOR NURSES AND PHARMACISTS

The advent of supplementary prescribing for nurses and pharmacists in the UK (Department of Health, 2003) has created two new groups of prescribers who can potentially prescribe high-dose antipsychotic medication. Supplementary prescribing allows nurses and pharmacists who have completed an approved training course and undergone a period of supervised practice to prescribe antipsychotic and other drugs in the context of an agreed partnership between the supplementary prescriber and the independent prescriber (i.e. the psychiatrist) to implement an agreed, patient-specific clinical management plan with the patient's agreement. There are very few restrictions on supplementary prescribers, who can thus prescribe antipsychotic regimes outside *BNF* limits, provided that their prescribing is covered by a patient's clinical management plan.

NURSES AND HIGH-DOSE TREATMENT REGIMENS

Although nurse prescribing is in its infancy in the UK, nurses remain overwhelmingly the largest single professional group in the UK mental health workforce. Nurses are intimately involved in caring for patients receiving high-doses of antipsychotic medication for treatment-resistant schizophrenia. Nursing these patients is often a difficult and demanding task, requiring relevant psychological skills as well as a safe and appropriate environment in which to practice. Also essential are staffing levels that permit nurses to offer patients individual time and attention on a daily basis. The use of high doses of antipsychotic medication cannot substitute for skilled nursing care, which should be synergistic with pharmacological treatments. Nurses can be seen to have a dual role with regard to high-dose medication regimens, both to advocate on the patient's behalf for safe and effective prescribing and also to administer and monitor prescribed treatment regimens. The successful fulfillment of both these roles demands an assertive, well-educated and knowledgeable nursing workforce.

Nurses are responsible for the bulk of the day-to-day monitoring of the efficacy and side-effects of high-dose regimens. A number of studies (Gray *et al*, 2001, 2002*a,b*, 2003) have demonstrated that training nurses

in the use of validated clinical instruments such as the Liverpool University Side-Effect Rating Scale (LUNSERS: Day *et al*, 1995), the Simpson Angus Extrapyramidal Side-Effect Rating Scale (EPSE: Simpson & Angus, 1970), the Barnes Akathisia Rating Scale (BARS: Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS: Guy, 1976) can help improve side-effect monitoring and management. Similarly, the employment by nurses of instruments such as the Brief Psychiatric Rating Scale (BPRS: Lukoff *et al*, 1986) may improve the monitoring of patients symptoms (McGorry *et al*, 1988; Acorn, 1993) and thus the efficacy of treatment regimens. Nurses are also well placed to deliver psychoeducation to these patients and to use motivational interviewing and other techniques which have been demonstrated to improve patients' adherence to prescribed treatment regimens (Gray *et al*, 2001, 2002a,b, 2003). The more widespread adoption by nurses of structured clinical instruments, such as those described above, seems likely to increase the safety of high-dose treatment for patients, although as yet there is no trial evidence to support this.

Service implications

- Organisational pressures on throughput of patients can be high in acute settings, particularly in inner city districts. Management and staff need to be made aware that such a situation may lead to an increased use of high-dose strategies in an attempt to facilitate swift clinical improvement. Local service protocols should exist, covering the use of high-dose antipsychotic medication, the management of treatment resistance and emergency tranquillisation. They should be derived from this consensus statement and consistent with NICE guidance (National Collaborating Centre for Mental Health, 2002). Such service protocols should take account of local circumstances and should be developed by a group comprising representatives from psychiatry, nursing, pharmacy, psychology, occupational therapy and patients and carers.
- Information systems should alert prescribers to running total daily doses and to potential drug interactions.
- Regular staff training and re-training in the use of de-escalation and aggression management techniques.
- The provision of sufficient clinical and environmental resources to minimise the need for high-dose medication; these should include:
 - adequate nurse : patient ratios
 - adequate numbers of properly staffed residential treatment and care facilities
 - adequate quantity and quality of space within which seriously ill patients can be nursed.
- Admission and intensive care units should be properly equipped for ECG and blood pressure monitoring, and should have ready access to a clinical biochemistry laboratory.
- Time and costs should be explicitly identified and met to enable continuing staff education in the management of psychosis, and the induction of new staff.

Resource implications

Several of the suggestions and recommendations contained in this revised consensus statement carry with them resource implications, both in terms of financial costs (recurring and non-recurring) and opportunity costs in terms of staff time. The essential message is that the use of high-dose antipsychotic medication cannot be justified as a general clinical strategy, but equally the recognition that in a small proportion of cases such a practice could be justified, provided certain important procedures relating to safety and effectiveness are carefully observed. The resource implications in in-patient services fall broadly into two categories; those related to minimising the need for high-dose medication, and those related to the safe use of high dosage if and when required.

SAFE AND APPROPRIATE USE OF ANTIPSYCHOTIC MEDICATION

The main factors that may require increased resources are the need for time over which to assess response, the need for adequate staff-to-patient ratios, adequate staff training in assessment and non-pharmacological interventions, and the provision of properly designed facilities in sufficient quantity (see also chapter on Service implications). The use of high dose should not be a substitute for assessment, treatment and care of the highest quality and the issue is therefore the economics of clinical governance with regard to antipsychotic drugs.

STAFFING

- Consultant presence: for regular and frequent review of the treatment plan.
- Nursing levels for safe and effective care, assessment and intervention, including cognitive-behavioural therapy.
- Professions supplementary to medicine, and clinical psychology, as for nursing.
- Clinical pharmacy, for example, input to treatment plans and working with clinical teams to raise awareness of high-dose prescribing.

EDUCATION AND TRAINING

- Training in effective psychotherapeutic techniques, such as cognitive-behavioural therapy.
- Awareness of the issues around the safety of antipsychotic drugs.
- Training in de-escalation and aggression management techniques.
- Training in ECG interpretation.
- Regular training in cardiopulmonary resuscitation techniques.
- Knowledge of relevant guidelines, standards, and summaries of product characteristics.

PHYSICAL ENVIRONMENT

- Adequate built facilities, including in-patient and day care places.
- Ward design and fitting out to take account of the need for good observation, space, privacy, quiet areas, ventilation, and low-risk fixtures.

EQUIPMENT AND PROCEDURES

- Up-to-date and reliable ECG equipment.
- Ready access to ECG interpretation by a cardiologist.
- Suction and resuscitation equipment.
- Provision for plasma drug assays, if required to monitor adherence.
- Ready availability of relevant guidelines.

DRUG COSTS

- Possibly greater use of clozapine: see National Institute for Clinical Excellence (2002) Technology Appraisal Guidance, No. 43, *Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia*.

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Appendix: Relevant national and other treatment guidelines

- Management of Imminent Violence: Clinical Practice Guidelines to Support Mental Health Services* (Royal College of Psychiatrists College Research Unit, 1998)
- National Institute for Clinical Excellence Clinical Guideline 1. *Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care* (National Collaborating Centre for Mental Health, 2002)
- National Institute for Clinical Excellence Clinical Guideline 25. *Violence: the Short-term Management of Disturbed/Violent Behaviour in In-patient Psychiatric Settings and Emergency Departments* (National Collaborating Centre for Nursing and Supportive Care, 2005)
- National Institute for Clinical Excellence Technology Appraisal Guidance, No. 43. *Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia* (National Institute for Clinical Excellence, 2002)
- The Maudsley 2003 Prescribing Guidelines* (Taylor, et al, 2003)
- Treatment of Schizophrenia: The Expert Consensus Guideline Series* (McEvoy, et al, 1999)
- Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia*. Working Group for the Canadian Psychiatric Association & the Canadian Alliance for Research on Schizophrenia (1998)
- Practice Guidelines for the Treatment of Patients with Schizophrenia* (American Psychiatric Association, 1997)
- The Royal Australian and New Zealand College of Psychiatrists (RANZCP) Clinical Practice Guidelines. *Summary Australian and New Zealand Clinical Practice Guideline for the Treatment of Schizophrenia* (McGorry et al, 2003)