

CR190

The risks and benefits of high- dose antipsychotic medication

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COLLEGE REPORT

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The risks and benefits of high-dose antipsychotic medication**

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Membership of the Consensus Working Group

2023 revision

Dr Ravindra B Belgamwar

Consultant Psychiatrist/ Hon.
Senior Lecturer/ R&D Director Care
TPD Adult Psychiatry higher training
West Midlands

Prof Oliver Howes

Professor of Molecular Psychiatry,
King's and Imperial Colleges

Dr Angharad de Cates

Wellcome Trust Clinical Doctoral Fellow at the
University of Oxford, and Honorary Specialty
Registrar at Oxford Health NHS FT

Professor Hamish McAllister-Williams

Northern Centre for Mood Disorders,
Newcastle University Translational and
Clinical Research Institute, Newcastle, UK;
Cumbria, Northumberland, Tyne and Wear
NHS Foundation Trust

Professor Claudia Cooper

UCL and Camden and Islington NHS
Foundation Trust

Dr Sam Chamberlain

Professor of Psychiatry, University of
Southampton

Dr Sarah Markham

King's College London

Original guideline (2014)

Thomas R. E. Barnes

Professor of Clinical Psychiatry Imperial
College London and West London Mental
Health NHS Trust

Stephen Dye

Consultant In-Patient Psychiatrist
Norfolk and Suffolk NHS Foundation Trust

Nicol Ferrier

Professor of Psychiatry Newcastle University,
Newcastle

Richard Gray

Professor of Nursing and Assistant
Executive Director Research Hamad Medical
Corporation, Doha, Qatar

Peter M. Haddad

Consultant Psychiatrist
Greater Manchester West Mental Health NHS
Foundation Trust, Salford

Oliver Howes

Reader/Group Head
MRC Clinical Sciences Centre, Imperial
College, Hammersmith Hospital and Institute
of Psychiatry, King's College London

Eileen Joyce

Professor of Neuropsychiatry University
College London

David Cunningham Owens

Professor of Clinical Psychiatry University of
Edinburgh

Maxine X. Patel

Clinical Senior Lecturer, Institute of Psychiatry,
King's College London

Carol Paton

Chief Pharmacist, Oxleas NHS Foundation Trust

James Stone

Clinical Senior Lecturer, Imperial College
London and West London Mental Health
NHS Trust

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Executive summary

This report reflects the consensus views of a group of clinicians on the risks and benefits of high-dose antipsychotic medication for a range of clinical indications for which antipsychotic medication is commonly used in psychiatric practice. For each of these indications, the members of the Consensus Working Group took account of the evidence from the published literature and their clinical experience and considered the clinical implications. While there is little convincing evidence that off-label prescription of doses of antipsychotic medication above the licensed dosage range has any therapeutic advantage in any clinical setting, there is clear evidence for a greater side-effect burden and the need for appropriate safety monitoring. The key recommendation is that any prescription of high-dose antipsychotic medication should be seen as an explicit, time-limited individual trial with a distinct treatment target. There should be a clear plan for regular clinical review including safety monitoring. The high-dose regimen should only be continued if the trial shows evidence of benefit that is not outweighed by tolerability or safety problems.

We recommend that clinicians consider the patient and carer perspective when applying the guidance in their practice. In particular, the guidelines should be implemented in the context of shared decision-making and care-planning regarding treatment aims, taking into account the patient's wishes, preferences and their past experiences of what works and what doesn't work when being prescribed antipsychotic medication. This will help develop and maintain a positive therapeutic alliance between the patient and their doctor. It will also promote mutual relational and epistemic regard between the patient and clinician.

Abbreviations

BNF	British National Formulary
ECG	Electrocardiogram
EPS	Extrapyramidal side-effects
MCA	Medicines Control Agency
NAS	National Audit of Schizophrenia
NMS	Neuroleptic malignant syndrome
PICU	Psychiatric intensive care unit
POMH-UK	Prescribing Observatory for Mental Health
PORT	Patient outcomes research team
PRN	pro re nata: as required
RCT	Randomised controlled trial
RR	Relative risk
SPC	Summary of Product Characteristics
SPECT	Single-photon emission computed tomography
TdP	Torsade de pointes

Definition of high dose

Antipsychotic monotherapy

In order to receive a marketing authorisation (previously known as a product licence), a drug requires extensive preclinical (animal) and clinical (human) studies to be completed. The findings are submitted to the Medicines and Healthcare Products Regulatory Agency in the UK, or to the European Medicines Agency if a pan-European marketing authorisation is being sought. A panel of experts carefully considers the efficacy and safety data and, if acceptable, a marketing authorisation is granted. The Summary of Product Characteristics (SPC) 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 maximum licensed dose in the SPC can differ across the age range, generally being lower in children, adolescents and the elderly than in working-age adults. It might also be specific to clinical indications within age groups. For example, the maximum licensed dose of quetiapine (immediate-release tablets) for the treatment of schizophrenia in adults is 750 mg/day, whereas for the treatment of mania it is 800 mg/day. This reflects the doses used in the respective phase III clinical trials programmes that underpinned the marketing authorisation. For a single antipsychotic, the Consensus Working Group defined a high dose as one that exceeds the maximum dose stated in the manufacturer's SPC for that drug (with respect to the age of the patient and the indication being treated).

The SPCs of older, first-generation ('typical' or 'conventional') antipsychotics often refer to broader clinical indications and wider dosage ranges than the SPCs of newer antipsychotics (those marketed in the past 15 years). As new data emerge, the dosage recommendations in the SPC can change to reflect this new knowledge. For example, the maximum dose of 240 mg/day of oral haloperidol, previously authorised for treatment-resistant schizophrenia 'in extreme cases', has been revised downward substantially over time. Prescribing a dose higher than is stated in the SPC is likely to exceed the acceptable risk–benefit ratio for the drug and constitutes off-label use. It is the prescriber (along with the pharmacist who dispenses the prescription and the nurse who administers the medication), rather than the manufacturer, who assumes responsibility for any subsequent harm to the patient.

The dosage recommendations in the [British National Formulary \(BNF\)](#) largely reflect those in product SPCs, although expert clinical opinion can also influence the advice given. For example, in edition 20 (September 1990) of the BNF, 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 edition 28 (September 1994) was published, more was understood about the pharmacology of antipsychotics, the use of clozapine in treatment-refractory schizophrenia had been established and the Royal College of Psychiatrists had published a consensus statement on the use of high-dose antipsychotic medication (Royal College of Psychiatrists, 1993). As a result, this statement did not appear in edition 28 of the BNF and was replaced by a summary of good practice points relating to the prescribing and monitoring of high-dose regimens.

The SPCs for antipsychotics can change at any time in line with new data. The online version of the BNF is updated monthly but, even so, the BNF might not always reflect the results of recent clinical trials or the refinement of antipsychotic use in practice. This is particularly likely for recently introduced antipsychotics. Despite these limitations, the BNF is still the most user-friendly and widely used source of basic prescribing information in the UK. Antipsychotic doses that are above the maximum stated in the BNF ('above BNF limits'), with respect to the age of the patient and the indication being treated, can therefore be described as high dose.

Combined antipsychotics/antipsychotic polypharmacy

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

- 1 By converting the dose of each drug into 'chlorpromazine equivalents' mg/day and adding these together. A cumulative dose of more than 1000 mg/day (i.e., the maximum SPC daily dose for chlorpromazine) in chlorpromazine equivalents is a high dose.
- 2 By converting the dose of each drug into a percentage of the BNF maximum recommended dose for that drug and adding these together. A cumulative dose of more than 100% is a high dose.

Both of these methods are essentially arbitrary and have limitations. Chlorpromazine equivalents were developed on the basis of a combination of limited clinical evidence, expert consensus, and the relative potency of antipsychotics in blocking accepted table of chlorpromazine equivalents: different sources give different equivalent doses (Patel et al., 2013). Psychiatrists' understanding of equivalent doses in clinical practice is often different again, and might change over time, and there is no easy method for converting doses of second-generation ('atypical') antipsychotics into chlorpromazine equivalents. In addition, a high dose calculated by this method might bear little resemblance to the maximum dose in the SPC.

The second method, adding the percentage of the BNF maximum dose for each drug, is simpler in that the BNF maximum dose is clearly stated for every antipsychotic drug (except trifluoperazine). However, one problem with this approach is that it takes no account of the use of combined antipsychotic drugs with contrasting mechanisms of

action (such as augmenting clozapine with a second antipsychotic such as amisulpride or sulpiride), which might affect therapeutic efficacy or side-effects and tolerability. Thus, because of possible pharmacodynamic and pharmacokinetic interactions, the effects of such combinations might not reflect a simple addition of percentages of their respective maximum dose. Further, some combinations of antipsychotic drugs have a greater potential for side-effects. For example, a prescription for flupentixol depot 400 mg/week and chlorpromazine 1000 mg/day would be 200% of the BNF maximum, as would a prescription for olanzapine 20 mg/day and aripiprazole 30 mg/day. But it is unlikely that these two combinations would be equally safe and tolerable.

The Consensus Working Group took the following as a definition of high dose: a total daily dose of a single antipsychotic which exceeds the upper limit stated in the SPC or BNF with respect to the age of the patient and the indication being treated, and a total daily dose of two or more antipsychotics which exceeds the SPC or BNF maximum using the percentage method.

Prevalence and nature of high-dose antipsychotic regimens in clinical practice

The Prescribing Observatory for Mental Health (POMH-UK) organised a clinical audit of antipsychotic use in 2012, involving 9537 patients prescribed antipsychotic medication in 48 mental health trusts, and found that around a quarter of the sample were prescribed high-dose antipsychotic medication (POMH-UK, 2012).

Around a quarter of patients on acute adult or forensic wards were prescribed high-dose antipsychotic medication. The majority (86%) of high-dose prescriptions involved combined antipsychotics, and approximately two thirds of these combinations included an antipsychotic prescribed PRN (pro re nata: as required). Further analysis of POMH data from 2172 episodes of acutely disturbed behaviour from 58 mental health trusts found that benzodiazepines were more likely to be prescribed in this situation than antipsychotics; except when physical violence had been exhibited, when both were generally prescribed. In one quarter of episodes, patients remained extremely active in the hour after rapid tranquilisation (Paton et al., 2018).

In a further POMH audit of the use of antipsychotic medication in 2017, 57 Trusts submitted data on 5159 patients from acute/PICU clinical teams, 38 Trusts submitted data on 1350 patients from rehabilitation/complex needs clinical teams, and 46 Trusts submitted data on 3563 patients from forensic clinical teams. Of the total national sample of 10072 patients, one in ten was prescribed regular high-dose antipsychotic medication, only a third of whom had the high-dose prescription documented in their care plan. Physical health monitoring was generally good for these patients on regular, high-dose antipsychotic medication, but antipsychotic-induced movement disorder had not been documented as assessed in the last year for about a third. The data revealed that the reduction in the prevalence of use of combined antipsychotic medications over time could be largely attributed to fewer prescriptions for PRN antipsychotic medication.

The most common clinical reasons for prescribing regular combined antipsychotic medication differed across the clinical settings. For inpatients in acute adult ward/PICU settings, the most common reasons were a poor response to antipsychotic monotherapy or the overlap period while switching from one antipsychotic to another. For patients in forensic and rehabilitation/complex needs services, the most common reason was the augmentation of clozapine with a second antipsychotic; in three-quarters of such cases, the augmenting antipsychotic was amisulpride or aripiprazole.

Also in 2012, the National Audit of Schizophrenia (NAS) gathered data on antipsychotic prescription patterns from the clinical records of 5091 patients in 60 mental health trusts

(Royal College of Psychiatrists, 2012). This sample differed from the POMH-UK sample in that it predominantly comprised community patients under the care of community mental health teams (n = 3545), Assertive Outreach teams (n = 615) and early intervention services (n = 286); nearly half of the total sample were aged between 45 and 64 years. The NAS did not collect data on antipsychotic PRN prescribing; however, in these particular clinical settings, the prescription of PRN antipsychotics might be assumed to be far less common than in the POMH-UK sample. This might partly explain why only 10% (95%CI, 9.3–10.9%) of patients in the NAS prescribing dataset sample (n = 5055) were prescribed high-dose antipsychotic medication and only 16% were prescribed more than one antipsychotic medication at a time (Patel et al., 2014). But another likely explanation is that clinicians use lower, regular doses for maintenance treatment than they do for patients who are acutely unwell. Indeed, the total mean antipsychotic dose, expressed as a percentage of the maximum dose stated in the BNF, was 59% (95%CI, 57.7–60.4%); the 16% receiving antipsychotic polypharmacy had a higher mean dose than those prescribed a single antipsychotic (98.9 v. 51.0%, $P < 0.001$; Patel et al., 2014). The first update of the NAS occurred in 2013-2014: examining a database of 5608 records from all 64 Trusts / Health boards (NAS 2014). The findings largely were unchanged from the 2012 audit.

The pharmacological basis for high-dose antipsychotic prescribing

From a pharmacological perspective, there are two main reasons why higher doses of antipsychotics might be theoretically justified in some cases. First, insufficient drug might reach the effect site because of individual patient differences in pharmacokinetics; second, differences at the effect site in some patients (pharmacodynamic differences) might mean that high doses of drug are required. The evidence for each is summarised below.

There are several possible explanations why insufficient antipsychotic drug might reach the D2 receptors in the brain: drug plasma levels could be insufficient because of inadequate absorption and/or rapid metabolism, or there could be poor penetration across the blood–brain barrier. Studies of drug plasma levels in patients taking antipsychotic drugs certainly show that there is considerable variability between individuals (Brockmoller et al., 2002; Patel et al., 2011; Bowskill et al., 2012a, 2012b; Handley et al., 2013). Levels of smoking, caffeine consumption and genetic variation – for example, in cytochrome P450 enzymes that metabolise antipsychotic drugs – all contribute to this variation (Kelly et al., 2006; Bigos et al., 2011; Uchida et al., 2011). In general, antipsychotic plasma levels show a close relationship to D occupancy and low drug plasma levels result in low D2 occupancy (Uchida et al., 2011; Kim et al., 2012) and there is evidence that plasma levels are linked to clinical response for a number of antipsychotics (Sparshatt et al., 2009, 2010, 2011; Bishara et al., 2013). Thus, where plasma levels are low and there is an established relationship between plasma levels and response, there is a pharmacological rationale for increasing the dose of the antipsychotic to obtain adequate plasma levels. Of course, an alternative strategy might be to address modifiable factors that underlie low plasma levels, such as, for certain antipsychotics, reducing smoking (Sharif, 2003; Rostami-Hodjegan et al., 2004; Taylor, 2009). If high-dose strategies are used, it is necessary to warn the patient that changes in these modifiable factors, such as stopping smoking, might result in very high plasma levels. An important caveat is that the nature of the relationship between plasma levels and clinical response is not clearly established for the majority of antipsychotic drugs.

All currently licensed antipsychotic drugs act on dopamine D2 receptors. In vitro studies in the 1970s found that there was a close relationship between the clinical potency of antipsychotic drugs and their affinity for D2 receptors (Seeman & Lee, 1975; Seeman, 1987). Subsequent in vivo molecular imaging studies for a range of antipsychotics have shown that occupancy of D2 receptors in the brain is required for a drug to have a therapeutic effect (Nordstrom et al., 1993; Kapur et al., 2000). Molecular imaging studies have also found that there is a relationship between D2-receptor occupancy and clinical response (Nordstrom et al., 1993; Kapur et al., 2000). It would seem that below an occupancy level of around 65%, a therapeutic response is unlikely, and that no further response is likely to be achieved by an increase in the occupancy level above 80%.

A potentially important avenue of research will be the delineation of D2-receptor occupancy

levels in various regions of the brain and the optimal duration of D2-receptor blockade for individual patients (Pani et al., 2018). Molecular imaging studies examining occupancy at other receptors in vivo at standard clinically effective doses have found that occupancy at 5-HT_{2A} receptors and D₁ receptors varies markedly between different antipsychotic medications, despite similar D2-receptor occupancy and clinical efficacy (Reimold et al., 2007). This suggests that the action of antipsychotics at 5-HT_{2A} and D₁ receptors does not underlie clinical response, although their action at these receptors might nevertheless be important for side-effects. However, not all receptors to which antipsychotic medications bind have been studied in vivo, so a role for these cannot be excluded. Clinical studies with very selective D2-antagonist drugs, such as amisulpride, have found them to be as effective as broad action antipsychotics such as olanzapine but differences in side effects between different agents are more marked than differences in efficacy (Kahn et al., 2008; Komossa et al., 2010; Leucht et al., 2013; Huhn et al., 2019).

Some newer antipsychotics such as aripiprazole and cariprazine have a novel action: partial agonism at D₂ receptors. However, their D₂-receptor occupancy is higher than for dopamine antagonist antipsychotics at clinically effective doses (Kegeles et al., 2008; Kaar et al., 2020). Given aripiprazole's weak partial agonism, and probably the same with cariprazine, the overall D₂ blockade is about the same as seen with other antipsychotics (Mamo et al., 2007). This fits well with the evidence that the dopamine system is abnormal in schizophrenia, and the evidence that links hyperdopaminergic activity to symptoms (Howes et al., 2007; Howes & Kapur, 2009). Thus, D₂ receptors may be considered the main site of therapeutic action of antipsychotic medication in the brain (Kapur & Remington, 2001).

The other factor that might underlie the need to use high dosage is differences at the drug effect site in some patients. One possibility is that some patients have higher D₂ receptor levels or altered D₂-receptor function. However, antipsychotic-naïve patients with schizophrenia do not show a consistent alteration in D₂-receptor availability (Howes et al., 2009, 2012a). While it remains possible that there is a subgroup of patients who have a marked elevation in D₂-receptor availability or alterations in receptor function, there is currently little in vivo biological evidence that this is the case. Another possibility is suggested by the molecular imaging studies that show that some patients do not respond despite high levels of antipsychotic D₂ occupancy (Nordstrom et al., 1993; Kapur et al., 2000). This indicates that there are some patients in whom D₂ occupancy is not sufficient for clinical response. Coupled with findings that there is lower response to antipsychotic treatment in patients with less dopamine dysfunction (Abi-Dargham et al., 2000; Demjaha et al., 2012), this evidence suggests that the pathophysiology underlying schizophrenia is non-dopaminergic in a proportion of patients. Clearly there would be no point in using high doses of antipsychotic drugs if this were the case.

On balance, there is a reasonable amount of evidence to support the first rationale for high-dose prescribing: that is, that pharmacokinetic differences mean there are low drug plasma levels and insufficient antipsychotic blockade of D₂ receptors at standard doses in some patients. However, at present, plasma antipsychotic level monitoring, with the exception of clozapine, is not part of routine clinical practice and its effectiveness in such a context has yet to be determined. With regard to the second rationale, there is currently little evidence to support the notion that there are differences in D₂-receptor levels or function in some patients that necessitate the use of high doses. Furthermore, given the evidence that some patients do not respond despite high levels of D₂ occupancy, there is little basis for high doses in patients with adequate plasma levels.

Why do clinicians prescribe high-dose antipsychotics?

Clinicians treating schizophrenia often prescribe high doses. Poor response of the illness to standard treatment is a relatively common reason. Howes et al (2012b) found that prior to commencing clozapine, over a third of patients had received antipsychotic medication above the licensed maximum dose and a similar proportion had been prescribed antipsychotic polypharmacy.

Patient factors predicting the use of high dosage include younger age, longer duration of illness and a history of violence and aggression (Chaplin & McGuigan, 1996; Tyson et al., 1999; Wilkie et al., 2001; Lelliott et al., 2002; Bitter et al., 2003; Hung & Cheung, 2008; Paton et al., 2008; Sim et al., 2009), although the severity and symptom profile of the illness, level of medication adherence, amount of carer support and other psychosocial factors might plausibly have some influence in individual cases. UK studies have not yielded any clear relationship between dosage and ethnicity (Connolly & Taylor, 2008; Paton et al., 2008; Connolly et al., 2010).

Factors relating to prescribers include limited psychopharmacological knowledge and scepticism about prescribing algorithms (Wilkie et al., 2001; Harrington et al., 2002; Ito et al., 2005). However, the most potent prescriber factor contributing to high dosage is the use of combined antipsychotics (Hung & Cheung, 2008; Paton et al., 2008; Roh et al., 2014). There are several clinical rationales for prescribing combined antipsychotics (Sernyak & Rosenheck, 2004; Barnes & Paton, 2011), including attempting to enhance or speed up the therapeutic effect, managing challenging symptoms such as behavioural disturbance and aggression or targeting a particular symptom or symptom domain such as affective instability. There is also some evidence that the addition of aripiprazole to certain antipsychotics can treat raised prolactin levels and metabolic dysregulation caused by the primary antipsychotic (Gallego et al., 2012). Further, in one long-term observational study, the use of antipsychotic combinations for schizophrenia, particularly those including clozapine and depot/LAI antipsychotic preparations, were associated with a slightly lower risk of psychiatric rehospitalisation than monotherapy (Tiihonen et al., 2019). Specifically, aripiprazole added to clozapine was associated with the lowest risk of rehospitalisation over the 20-year follow up (14% vs 23% with clozapine alone). One possible explanation is that the combination of aripiprazole with clozapine has better tolerability than clozapine alone, through reducing sedation and the metabolic effects of clozapine. Nevertheless, in most cases antipsychotic combinations are likely to increase the side-effect burden, compared with monotherapy. Overall, the evidence from randomised controlled trials (RCTs) to support the use of combined antipsychotics in schizophrenia remains scarce (Barnes & Paton, 2011; Ballon & Scott, 2013).

Sometimes high dosage might be inadvertent, and clinicians might not even be aware of it. This could result, for example, from successive, incremental increases in dose

at times of symptom exacerbation that are not subsequently reduced, or from the prescription of more than one antipsychotic that, although the dose of each individual drug is below the licensed maximum, together constitute high dosage. Further, for patients on continuing antipsychotic treatment, a depot/long-acting injection and an oral antipsychotic are commonly co-prescribed, the latter being added, perhaps, to allow for greater flexibility in dosage titration. Audits of antipsychotic use by POMH-UK found that such combinations often lead to high-dose prescribing (Barnes et al., 2009).

First-episode psychosis

Background

There is a growing move for pharmacotherapy in psychosis to be considered specific to the stage of illness in the treatment of schizophrenia (Remington, 2005). In most centres, current practice is to commence treatment at the first episode with a second-generation antipsychotic drug, although some have suggested that the side-effect profile of some first-generation antipsychotic medications might have some benefits over some of the newer agents in terms of weight gain and metabolic syndrome, and that low to moderate doses of low-potency, first-generation antipsychotics such as perphenazine might have a similar propensity for extrapyramidal side-effects (EPS; Miller et al., 2008). The reality is that both the first- and second-generation groups have similar side-effect profiles and the division of antipsychotics into these two groups carries the risk of obscuring the differences in side-effects between individual drugs (Leucht et al., 2013).

Evidence for efficacy

In terms of dosing in first-episode psychosis, patients are generally responsive to treatment, with a reported 80% response to antipsychotic treatment at low to standard treatment doses, so high-dose strategies should rarely be required, if at all (Remington et al., 1998; Robinson et al., 1999; Remington, 2005). There is considerable evidence that low doses of either first- or second-generation antipsychotics are effective in achieving symptomatic and functional improvement and acceptable to first-episode patients (McEvoy et al., 1991; Zhang-Wong et al., 1999; Lieberman et al., 2003; Huq, 2004; Schooler et al., 2005; Kahn et al., 2008). It has been suggested that the use of benzodiazepines rather than high-dose antipsychotic drugs might be preferable for the management of hostility (Remington et al., 1998; McGorry et al., 2013), although according to a recent Cochrane review there is insufficient evidence to support or refute using benzodiazepines alone or in addition to other medications (Zaman et al., 2017).

Nonetheless, high doses of second-generation antipsychotic drugs have been tested in some patients with first-episode psychosis, in an attempt to improve the proportion of response (Agid et al., 2011). Increasing dose in stages, up to a 'high dose' of olanzapine 22.5–30.0 mg daily or risperidone 6.5–10.0 mg daily improved response to initial treatment over standard doses by only 4%, from 71 to 75% (Agid et al., 2011). Switching the patients whose illness did not respond to treatment to an alternative, second-generation antipsychotic drug led to an improvement in 17% (i.e., a further 4% of the original sample). Of the 50 remaining patients whose illness did not respond to treatment, 28 agreed to a switch to clozapine, and 75% of these 28 improved (9% of the original sample).

A study of medication use in patients from Denmark with first-episode psychosis reported a growing trend between 1995 and 2005 for antipsychotic polypharmacy, with up to 50% of first-episode patients receiving two or more antipsychotic drugs (Nielsen et al., 2010). This led to an average antipsychotic use that was double the daily recommended treatment dose in these patients. The reason for this increase in the use of combined

antipsychotics is not clear, but it is important to note that it was also accompanied by overall improvements in measures of response to treatment such as admission to hospital. The improvement in outcome measures might also have been affected by other factors, however, such as the reported increase in outpatient contact over the same time period, and a reduction in the proportion of patients living alone (Nielsen et al., 2010).

Clinical implications

- There is no evidence that high-dose antipsychotic use is beneficial for patients with first-episode psychosis and such use should be avoided.
- Antipsychotic polypharmacy should be avoided. 'Top up' oral antipsychotic doses for patients on depot/long-acting injection medication should be used only as a short-term measure.
- Where antipsychotic response is poor, switching medication should be the preferred course of action, rather than increasing doses above BNF limits.
- Short-term benzodiazepine prescription has been suggested as preferable for the sedation of patients with aggression at this early stage of the illness.
- Clozapine should be considered in patients with first-episode psychosis who fail to show complete remission following adequate trials of two different antipsychotics.

Acute psychotic episode

Pharmacological rationale

Pharmacological studies have established a close relationship between the clinical potency of antipsychotic drugs and their affinity for receptors (Seeman & Lee, 1975; Creese et al., 1976; Seeman, 1987); all the currently available, effective antipsychotics share D2 blockade. Given the evidence that 'overactive dopamine release in the striatum is the proximal cause of psychotic symptoms' (Henn, 2011), antagonism at D2 receptors must be considered a plausible explanation for antipsychotic effects. Neuroimaging findings have allowed for a definition of a therapeutic window of between 65 and 78% D2-receptor occupancy in the striatum to achieve optimal therapeutic efficacy with the least side-effects (Kapur et al., 2000; Nord & Farde, 2011).

All other receptor actions are, in effect, non-target. For example, sedation, mediated by the anti-histaminergic or anti-adrenergic actions of an individual drug rather than by its key, or target, anti-dopaminergic action. Such effects vary markedly between drugs and individual patients.

Evidence for efficacy

The aims of drug treatment in the acute episode should be clearly articulated in a treatment plan. Typically, a plan would have the aims listed below.

- The improvement of psychotic symptoms, not least because of their negative impact on functioning and quality of life.
- The improvement of ancillary symptoms such as agitated or disturbed behaviour, affective features such as anxiety, and disturbed sleep.
- The treatment of possible emergency situations, with behavioural disturbance (see the chapter 'Acute violence and emergency tranquillisation').
- The minimisation and management of adverse effects.
- The maintenance of 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 in the belief that they would induce 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 rapidity or degree of response (Kane & Marder, 1993). Overall, attempts to achieve immediate high steady-state plasma levels have been shown to be unsafe and unnecessary (King, 1994). The current evidence suggests that response on standard dosage is relatively rapid, with the majority of improvement in the first year occurring in

the first month (Agid et al., 2003, 2006) and independent of dosage (Schennach-Wolff et al., 2011). Further, early lack of response seems to predict subsequent non-response: if symptoms have not shown a 20–25% improvement in mental-state rating-scale total score after 2 weeks at an appropriate dosage, the chance of a later response is slim (Lin et al., 2007; Kinon et al., 2008a).

With regard to second-generation antipsychotics, there have been two small, open-label trials of investigator-defined ‘high dose’ quetiapine (800–1200 mg/day) and risperidone (6–8 mg/day) in the treatment of acute schizophrenia. Both studies found these high doses were generally well-tolerated, with no serious side-effects (Pajonk et al., 2006; Raedler et al., 2006). There have also been two other randomised controlled trials of high-dose quetiapine versus placebo (Honer et al., 2011) and high-dose olanzapine versus clozapine (Meltzer et al., 2008). Honer and colleagues did not find any advantage for high-dose quetiapine, while Meltzer and colleagues found that high-dose olanzapine was similar in efficacy to clozapine in treatment-resistant schizophrenia. However, double-blind controlled trials demonstrating superior efficacy accompanied by a tolerable levels of side-effects would be required before high-dose, second-generation antipsychotic use could be recommended as a standard treatment.

The Consensus Working Group endorses the good-practice recommendations for the treatment of acute psychotic episodes as described in NICE Clinical Guideline 82: Schizophrenia: Core interventions in the treatment and management of schizophrenia in primary and secondary care (NICE CG178, 2014).

Switching medication

Clinicians tend to switch more often than they add another antipsychotic; clinical-trial data suggest that, over a year, approximately 30% of people with schizophrenia will have their antipsychotic medication changed (Kreyenbuhl et al., 2007; Bitter et al., 2008; Perez-Iglesias et al., 2008; Faries et al., 2009). While there is limited evidence of clinically relevant improvement in symptoms following switching, it can be a useful strategy to manage tolerability problems, as antipsychotics vary widely in side-effects (Haddad & Sharma, 2007). Some studies suggest that individuals who switch antipsychotics might have poorer clinical and economic outcomes than those who remain on their initial medication regimens (Lindenmayer et al., 2002; Weiden et al., 2006, 2007; Faries et al., 2009). Rosenheck et al (2009) reported that switching to a new antipsychotic yielded no significant improvement in symptoms, neurocognition, depression, quality of life or motor side-effects.

Schizophrenia symptoms often show an incomplete and fluctuating response to initial treatment. Careful monitoring of both response and side-effects in an adequate trial of the first antipsychotic is required as a basis for the decision to switch to a second drug. The risks of switching are destabilisation of the illness and the provocation of adverse effects, which could be related to several factors: withdrawal of the first antipsychotic, a response to the second antipsychotic, differences in pharmacological profile between the first and second drug (Lambert, 2007), or the period of polypharmacy while the drug treatments overlap, with the potential for high combined dosage. The best strategy for switching from one drug to another, in order to minimise adverse effects, including discontinuation

symptoms, has not been well examined empirically (Remington, 2005). One randomised trial comparing methods of switching from a first-generation antipsychotic 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). A gradual withdrawal of the first antipsychotic, more specifically a gradual cross-taper of the dosages of the first and second antipsychotics, is the most common recommendation (Lambert, 2007; Ganguli et al., 2008).

Clinical implications

- For the majority of people with acute psychotic illness, the target dose for effective treatment is likely to be below the licensed maximum.
- 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 not involve starting more than one antipsychotic at the same time.

Relapse prevention in schizophrenia

Pharmacological rationale

Jobe & Harrow (2005) critically reviewed the published, long-term, follow-up studies of people with schizophrenia, the majority of whom had been prescribed antipsychotic medication as well as receiving psychological and other treatments. They concluded that there is 'heterogeneity of long-term outcome, with between 21 and 57% showing good outcome, depending on the strictness of the criteria used to diagnose schizophrenia'. With regard to reduction in the risk of illness relapse, it is generally accepted that there is strong evidence for the efficacy of antipsychotic medication in first-episode patients and those with established illness in the short to medium term, the risk of relapse off medication being 2–6 times greater than with continued treatment (Leucht et al., 2003a, 2012a). Given the absence of reliable clinical predictors of prognosis or drug response, national guidelines have recommended pharmacological relapse prevention for all patients diagnosed with schizophrenia for 1–2 years (NICE, 2014). Bosveld-van Haandel et al (2001) reviewed relevant studies and concluded that antipsychotic treatment should be continued for longer than indicated by such guidelines. The administration of antipsychotic treatment long-term or indefinitely is common clinical practice, even though the case for such treatment is less sure: not everyone with a diagnosis of schizophrenia might require continuous antipsychotic medication for a prolonged period (Harrow & Jobe, 2013). Examining studies of maintenance treatment for schizophrenia, Leucht et al (2012b) found a statistically significant association between longer study duration and smaller relapse reduction by antipsychotic drugs compared with placebo, which might indicate some loss of efficacy over time. However, these reviewers emphasised that there were a host of other possible explanations for this 'counterintuitive' finding.

Long-term depot/long-acting injection antipsychotic maintenance treatment is at least as effective as oral medication for relapse prevention, if not superior (Kishimoto et al., 2014). A further meta-analysis of 32 RCTs, 65 cohort studies and 40 pre-post studies (Kishimoto et al., 2021) found significant benefit with depot/LAIs versus oral antipsychotic medication. There was a lower risk of hospitalisation/relapse for LAIs in all three study designs. This is despite the fluctuation in drug plasma level and degree of dopamine D2-receptor occupancy with long-acting injectable antipsychotic medication during the periods between injections, which led Boshes & Manschrek (2002) to argue that such treatment is essentially intermittent, and that its therapeutic effectiveness challenges the notion that continuously high dopamine D2-receptor blockade is necessary to prevent relapse in schizophrenia (Nyberg et al., 1995; Boshes & Manschrek, 2002).

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 the literature produced no consistent or robust findings (King, 1994). In fact, the 'neuroleptic threshold', the dose at which the first signs of EPS occur, is similar

in patients and healthy volunteers (haloperidol~4 mg), and the majority of patients will also show a therapeutic response to similar doses. It is the drug concentration in the brain rather than dose or drug plasma level that is important. With the advent of positron emission tomography, single-photon emission computed tomography (SPECT), and new radioligands, neuroimaging is now possible in vivo, but is currently usually only conducted under research conditions. SPECT neuroimaging is now possible in vivo in both patients and healthy volunteers and has become increasingly more sophisticated with the introduction of new radioligands (Talbot & Laruelle, 2002). Alternatively, drug plasma levels, at least with clozapine treatment, might go some way to increasing our understanding of dose optimisation while allowing for inter-individual variation in drug metabolism (Hiemke et al., 2011; Patel et al., 2011; Bowskill et al., 2012a; Couchman et al., 2013; Handley et al., 2013).

Evidence for efficacy

Studies of relapse prevention have tended not to test high-dosage regimens, rather, they 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 the first- generation antipsychotics, the recommended dose ranges are optimal for relapse prevention in psychotic illness, principally schizophrenia (Kane et al., 2002; Marder & Wirshing, 2003). Guidelines are consistent in their interpretation of the literature. The updated guidelines from the schizophrenia patient outcomes research team (PORT) recommend a maintenance dosage of 300–600 mg chlorpromazine equivalents daily for first-generation oral antipsychotics, partly on the basis that no advantage has been demonstrated for doses above 600 chlorpromazine equivalents (Krenyenbuhl, et al., 2010). For second-generation, oral antipsychotics, the PORT guidelines highlight that it has not yet been fully determined whether maintenance doses should be the same as doses used during the acute phase of illness. The systematic review showed no clinically significant improvements in efficacy with combination or high-dose more than one antipsychotics treatment strategies when compared with standard-dose monotherapy (CADTH, 2011). Similarly, the schizophrenia treatment guidelines from the World Federation of Societies of Biological Psychiatry (Hasan et al., 2013) conclude that there is ‘no good evidence that high maintenance doses are more effective in preventing relapse than standard doses. Therefore, a maintenance dosage below 600 CPZ equivalents is recommended’.

If patients with schizophrenia experience an exacerbation of psychotic symptoms despite receiving maintenance antipsychotic medication at a standard recommended dose, it is not uncommon for the dosage to be boosted in an attempt to treat the episode. It is unclear whether this is beneficial (Steingard et al., 1994; Kane & Leucht, 2008). It is also quite common for this increased dose not to be reduced subsequently, as the clinician hopes that the higher dosage will minimise the likelihood of a future exacerbation (Barnes et al., 2011). However, there is no convincing evidence base to support the prophylactic value of continuing the higher dose of antipsychotic medication long term or the prescription of further dose increments. Despite this lack of evidence for benefit, patients with a more refractory schizophrenic illness who experience repeated episodes over the years are not uncommonly prescribed accumulating increments in drug dose, leading to prolonged exposure to high dosage with its associated risks.

Compared with oral antipsychotics, depot or long-acting injections might increase the risk of excess dosage (Walkup et al., 2000). This seems to be particularly true when a combination of oral and depot antipsychotics are used (Barnes et al., 2009; Patel et al., 2014). Addressing the issue of depot medication pharmacotherapy for relapse prevention, the original NICE schizophrenia guideline (NICE, 2002) stated that 'For optimum effectiveness in preventing relapse, depot preparations should be prescribed within the standard recommended dosage and interval range'.

Clinical implications

- There does not seem to be any justification in the published literature for the use of high-dose antipsychotic medication for relapse prevention in schizophrenia.
- There is no convincing evidence that incremental increase of antipsychotic dose at times of psychotic relapse, with subsequent continuation of the new, higher dose, provides better relapse prevention in the long term.

Acute violence and emergency tranquillisation

Background

Use of psychotropic medication to quickly calm a severely agitated patient (in order to reduce the risk of imminent and serious violence to self or others, rather than to treat the underlying psychiatric condition) is referred to as rapid tranquillisation (Parker & Khwaja, 2011). Frequently, such medication is given to in-patients on a PRN basis in addition to regularly prescribed medication, and this can cause a patient to receive dosages above the licensed maximum (Baker, 2008; Paton et al., 2008; Barnes & Paton, 2011).

In these circumstances, medication should be part of a comprehensive approach to the management of violence, aggression and disturbed behaviour and used in association with or alongside assessment of the environment, strategies for de-escalation and use of other therapies for management of disturbed behaviour. NICE has produced guidelines on the management of disturbed behaviour (NICE, 2015) that include rapid tranquillisation as well as other management strategies: 'All medication given in the short-term management of disturbed/violent behaviour should be considered as part of rapid tranquillisation (including PRN medication).

In general, if medication is to be used for the management of disturbed behaviour, it should be offered orally initially. A number of antipsychotics and other types of medications are available in freeze-dried and standard oro-dispersible forms and liquids if necessary. If refused or inappropriate to the situation, then parenteral (intramuscular) medication (which has a faster onset of action with increased absorption) may be used. NICE (2014) suggest that intramuscular medication should be reserved for exceptional situations when other interventions 'have failed, been refused, judged not a proportionate response or are not indicated by previous clinical experience', but do not define a threshold for its use. The Maudsley guidelines describe rapid tranquillisation as 'essentially a treatment of last resort' to be used when other approaches have 'failed to de-escalate acutely disturbed behaviour' (Taylor et al., 2018). Although these guidelines are broad, both provide protocols that include offering of oral medication before proceeding to intramuscular injection and both mention specific drugs that might be used.

Evidence

As with seclusion and restraint, understandably there are very few robust studies that examine the safety and efficacy of medicines used within rapid tranquillisation, as it would be difficult to obtain valid consent from an individual at the time their behaviour warrants rapid tranquillisation. Much of the UK evidence comes from surveys or pragmatic research. One such study revealed that high dosage was predicted by damage to property and by violence while an in-patient, but the variation in use of intramuscular

medication between different services was greater than explained by differences in aggressive behaviour (Brown et al., 2010). Overall, there is a lack of evidence for any potential benefits in efficacy of high-dosage antipsychotic medication outweighing potential risks.

Tranquillisation means calming without sedation, although for acute behavioural disturbance, sedation might also be an appropriate strategy (Cunnane, 1994; Burgess, 1997; Battaglia et al., 2003; Citrome, 2004). Recently, there has been a general reduction in the range of doses of antipsychotics used for rapid tranquillisation and a move away from intravenous administration. Benzodiazepines and antipsychotics either alone or in combination (oral or intramuscular) have been widely studied and are commonly used. Benzodiazepines carry a risk of respiratory depression when used in high doses or in combination (Broadstock, 2001). Lorazepam has a shorter half-life than most other benzodiazepines and this might limit the risks associated with dose accumulation, making it a preferred choice in rapid tranquillisation. It is available as an oral or a parenteral formulation.

A Cochrane review concluded that there was insufficient evidence to determine whether benzodiazepine use, either alone or in addition to antipsychotics, was preferable to antipsychotics alone. Benzodiazepines may cause fewer side effects when administered alone, but additional side effects when used as adjuncts (Zaman et al., 2017). However, the potential use of benzodiazepines is especially relevant when considering medication use for acute distress in antipsychotic-naïve individuals.

The main areas of concern when using anti-psychotics for rapid tranquillisation are listed below.

- The majority of patients who receive rapid tranquillisation will already have been prescribed regular antipsychotic medication; the efficacy and tolerability of additional anti-psychotic medication or an additional dose of the same antipsychotic is untested.
- Induction of acute EPS: acute dystonia (potentially frightening and painful) and akathisia (inducing mental unease and potentially driving restless and impulsive behaviour) are more frequently associated with conventionally used first-generation antipsychotics, specifically intramuscular haloperidol, than with intramuscular second-generation antipsychotics in rapid tranquillisation (Satterthwaite et al., 2008).
- Neuroleptic malignant syndrome: this is unpredictable, is associated with considerable mortality risk, and can develop following a sudden increase in antipsychotic dosage and at high doses.
- Adverse cardiac events: although the relationship between antipsychotics, cardiac arrhythmias and sudden cardiac death is not straightforward, the prolongation of ventricular repolarisation (captured by the QT interval on an ECG) and subsequent increase in arrhythmic risk is generally dose related (Warner et al., 1996; Reilly et al., 2000; Ray et al., 2001) and associated with use of illicit drugs (Drake & Broadhurst, 1996; Pereira et al., 1997).

- Seizures: antipsychotics lower the seizure threshold and the risk is enhanced with rapid dose increases (which rapid tranquillisation implies), the presence of pre-existing organic brain disease, and phenothiazine use (Pisani et al., 2002).

High doses of antipsychotics are not recommended in rapid tranquillisation because of the risks already detailed, and also because other medicines should be used in this scenario. There is no categorical evidence that a sudden (parenteral) dose of antipsychotic is safe in a physically stressed patient. One review comparing second-generation antipsychotics for intramuscular use for agitation concluded that olanzapine and aripiprazole were less likely to cause EPS than haloperidol but called for further pharmacovigilance studies. It also acknowledged the limited applicability of the studies' results to a wider population, as the participants were not as severely unwell as those seen in clinical practice (Citrome, 2007). A meta-analysis found that in the treatment of agitation, intramuscular second-generation antipsychotics had a lower risk of acute EPS compared with haloperidol alone. However, intramuscular haloperidol plus promethazine had a risk comparable to that of intramuscular second-generation antipsychotics (Satterthwaite et al., 2008). The safety and efficacy of this combination is supported by more recent studies (e.g. Huf et al., 2010).

Zuclopenthixol acetate is particularly contentious, and it has been shown that there is wide variation in its use (Brown et al., 2010). A Cochrane review identified a dearth of evidence supporting its use, and noted that it is slow acting, with peak serum concentrations 36 hours after an injection, and a duration of action of 3 days (Gibson et al., 2004; Lacey et al., 2015). It is, therefore, no longer routinely recommended for rapid tranquillisation, as it would not be able to 'quickly calm the severely agitated patient in order to reduce the imminent and serious risk of violence'. Although NICE guidelines do not recommend zuclopenthixol acetate for rapid tranquillisation, it might be 'considered as an option' in certain circumstances (NICE, 2005). The Maudsley guidelines advise that zuclopenthixol acetate is not a rapidly tranquillising agent. It should be used only after an acutely psychotic patient has required repeated injections of short-acting antipsychotic drugs such as haloperidol or olanzapine, or sedative drugs such as lorazepam. It is perhaps best reserved for those few patients who have a prior history of good response to zuclopenthixol acetate (Taylor et al., 2018). Furthermore, it has been noted that a number of sudden deaths and fatal cardiac events have been reported to the Medicines Control Agency (MCA)/Medicines and Healthcare Products Regulatory Agency in relation to zuclopenthixol acetate (McAllister-Williams & Ferrier, 2002). However, its use is advocated by some clinicians for specific scenarios, with the rationale that the greater duration of action might reduce the need for repeated traumatic injections of shorter-acting medicines.

There have been large, randomised, unblinded trials in Brazil and India that investigated antipsychotics (either intramuscular olanzapine 10 mg or intramuscular haloperidol 10 mg) alone or, in the case of haloperidol, in combination with promethazine (TREC Collaborative Group, 2003; Alexander et al., 2004; Huf et al., 2007; Raveendran et al., 2007; Kishi et al., 2015). One of the outcome measures was the use of additional medication, but this is not explicit in relation to the use of additional antipsychotics as the studies also refer to medication needed to treat dystonic reactions. The main end-point used in the studies was that the patient was either 'tranquil' or 'asleep', rather than a response criterion in line with NICE's aim 'to achieve an optimal reduction in agitation and aggression, thereby allowing a thorough psychiatric evaluation to take place, while allowing comprehension and response to spoken messages throughout' (NICE, 2005).

One trial evaluated intramuscular olanzapine in comparison with a combination of haloperidol and promethazine (Raveendran et al., 2007). It found that olanzapine was more likely to calm patients (without inducing sleep) in under 1 hour; however, the effects wore off more quickly and resulted in this group requiring additional medical input. Haloperidol with promethazine was found to rapidly calm patients, with most asleep, and this was maintained over 4 hours. Huf et al (2007), in a trial of intramuscular haloperidol versus intramuscular haloperidol and promethazine, suggested that the routine use of promethazine has advantages, but the debate regarding patient outcomes of sleep versus a state of calm is ongoing in the UK. The TREC group has suggested that the combination of haloperidol and promethazine is more effective and safer than using antipsychotics alone and should thus be used as a comparator in any future studies (Huf et al., 2010). This suggestion is tempered by changes within the licence for haloperidol: reductions in the maximum oral and intramuscular daily doses and the recommendation of an electrocardiogram (ECG) prior to treatment (Janssen-Cilag, 2010). In view of this evidence, however, the use of haloperidol alone for first choice should probably be re-examined. Difficulties in obtaining and interpreting a pre-treatment ECG in an acutely disturbed patient should not be underestimated, and it might be that local policy-makers suggest obtaining an ECG 'at the earliest opportunity' for every patient admitted, or not using haloperidol at all in these circumstances.

Other antipsychotics licensed within the UK for intramuscular administration for acute management of disturbed behaviour are olanzapine and aripiprazole. Both have been shown to have a lower risk of EPS than haloperidol (Belgamwar & Fenton, 2005; Tran-Johnson et al., 2007). Parenteral benzodiazepines should not be given until at least 1 hour after intramuscular olanzapine (or vice versa) because of the possibility of cardiac and/or respiratory abnormalities, but benzodiazepines can be given concurrently with aripiprazole which itself produces improvements possibly specific to symptoms of core agitation, as opposed to non-specific sedation (Currier et al., 2007): repeated injections (if appropriate) are safe and well tolerated. This latter point highlights the benefits of using repeated small doses of medication, where possible, to titrate effects in a safe manner. This is established practice in other areas of medicine (e.g., pain relief/diabetic control) and substance misuse (e.g., opiate titration). Sliding scales of doses, adjusted according to clinical effect and physical condition, might well be an appropriate addition to a robust rapid tranquillisation policy. The benefits of this addition must be balanced against the risks of repeated injection with the patient potentially under restraint. All medications must be reviewed on a regular basis.

Thus, the gold standard for rapid tranquillisation has not yet been determined. All prescriptions for rapid tranquillisation should be tailored for the individual patient. There are numerous patient factors that affect choice of medication and dosage. These include relevant medical history and physical state (e.g., avoiding benzodiazepines in patients who have respiratory impairment, avoiding antipsychotics if possible in patients with dementia), other medication usage (including illicit substances and alcohol), previous response to rapid tranquillisation, any adverse drug reactions (e.g. neuroleptic malignant syndrome, acute dystonic reactions), and any existing advance directives/statements about medicines (Dye, 2011).

It should be remembered that rapid tranquillisation is not just administering medication; it also involves careful monitoring of patients and should be accompanied by psychosocial strategies to attempt to calm the patient. It has been shown that there are many

differences in standards for monitoring after intramuscular administration of medicines for rapid tranquillisation (Innes & Iyke, 2012, Paton et al., 2019). It has been suggested that pulse, temperature, blood pressure and respiratory rate should be monitored every 5–10 min for the first hour and then every 30–60 min until the patient becomes ambulatory (MacPherson et al., 2005). All this guidance creates challenges for the treating team, which some services have met using specific methods for patient safety (e.g. Metherall et al., 2006). It might be that rapid tranquillisation, used appropriately and effectively, can reduce the need for seclusion and physical restraint (Paterson & Leadbetter, 2004), but the good-practice principles of medication usage outlined in 'Clinical implications' (based on Parker & Khwaja, 2011) should be followed.

Clinical implications

- Rapid tranquillisation should only be used when careful clinical judgement is that the associated risks are less than the risks of not using rapid tranquillisation or employing non-pharmacological methods alone to manage disturbance (Coburn & Myck, 2009; Rossi & Swan, 2010). Lack of previous exposure to antipsychotic medication must be considered as well as possible illicit substance use. Another risk factor to be taken into account is a family history of sudden cardiac death (NICE, 2013).
- The aim of rapid tranquillisation is not to induce sleep or unconsciousness; the patient should be sedated but still able to respond to communication throughout and to participate in further assessment and treatment and (Battaglia et al., 2003; Citrome, 2004). The choice of medication and dosage should be individually tailored to the patient.
- The patient must be informed that medication is going to be administered and given the opportunity to accept oral medication voluntarily at all stages.
- Given the lack of evidence for use of high-dose medication and the proven associated risks, the lowest dose compatible with effective treatment should be used and BNF maximum doses (over a 24-hour period) only exceeded in rare circumstances and with caution, increased monitoring, and the advice of a consultant psychiatrist.
- The indication for which any PRN medication is prescribed should be explicit and clearly documented and all PRN medications should be reviewed on a regular basis.
- Oral and intramuscular medication should be prescribed separately.
- As few medicines as possible should be used.
- The use of combinations from the same class of medicine should be avoided wherever possible.
- Patients should be regularly monitored for clinical benefits and side-effects from administered medication.

Persistent aggression

Pharmacological rationale and evidence for efficacy

The evidence base for prescribing any medication (including antipsychotics) specifically to reduce violence in the medium to long term is limited (Goedhard et al., 2006). There is some evidence suggesting an association between higher antipsychotic dose in patients and a history of violence and/or recent violent behaviour (Krakowski et al., 1993; Chaplin & McGuigan, 1996; Wilkie et al., 2001) but the rationale for dose escalation is not clear. This lack of clarity might be because of the complexity of managing longer-term aggression, with its multifactorial causes: social and environmental factors, such as childhood conduct problems, victimisation history, social living situation and substance misuse (Swanson et al., 2008), can contribute independently of psychopathology. Aggression's multifactorial causes might also contribute to heterogeneity between and within different populations that are studied. Further, the definition of what constitutes 'persistent aggression' varies across research studies, covering a range of behaviours assessed with different measures.

Traditionally, first-generation antipsychotics have been used to treat patients with persistent aggression associated with psychosis (Buckley, 1999). The effectiveness of using first-generation antipsychotics in high doses for controlling persistent aggression is not proven. Akathisia has been found to be a risk factor for violence (Raja et al., 1997) and high doses might, therefore, increase the risk of persistent aggression by increasing the risk of akathisia. However, one study comparing aggressive and non-aggressive patients with schizophrenia found no statistical difference in the level of akathisia (Cheung et al., 1996).

Greater adherence to antipsychotic medication might be associated with reduced levels of aggression (Grinshpoon et al., 1998; Swanson et al., 2004, 2008; Arango et al., 2006). In a study comparing oral and depot zuclopenthixol, Arango et al (2006) found that treatment non-adherence was the best predictor of violence. Medication adherence reduced violence (except in patients with a history of childhood antisocial conduct). A similar finding was reported by Swanson et al (2008), who also found no difference between first- and second-generation antipsychotics in the reduction of violence in people with schizophrenia (although clozapine use was not examined in this study).

Clozapine has the best evidence base for an anti-aggressive effect (reviewed by Frogley et al., 2012, Victoroff et al., 2014). This effect was first demonstrated by Volavka et al (1993), and the majority of subsequent studies suggest that it is independent of antipsychotic or sedative effects or a decrease in other side-effects such as akathisia (this might be linked to its serotonergic effect). However, it has been recognised that the results were based mainly on statistical independence and on the observation that hostility diminishes despite only small changes in psychotic symptoms (Taylor & Estroff, 2003). The low number of RCTs available undoubtedly reflects the difficulty of performing such studies in this population, but those discussed by Frogley et al (2012) all reported preferential decreases on measures of aggression with clozapine (Niskanen

et al., 1974; Chow et al., 1996; Citrome et al., 2001; Volavka et al., 2004; Krakowski et al., 2006, 2008). The independence of an anti-aggressive effect was supported by the findings that, although clozapine was superior to olanzapine and haloperidol in reducing total aggression, olanzapine was associated with better neurocognitive functioning than the others and this better functioning was associated with a decrease in aggressive behaviour (Krakowski et al., 2008).

High doses of clozapine (1100 mg/day) have been observed to have beneficial effects in patients exhibiting threatening or aggressive behaviour and who rapidly metabolise clozapine (Maccall et al., 2009) but the safety and efficacy of a high-dose strategy have not been assessed in a controlled trial. There is also some evidence that clozapine's anti-aggressive effect might not be limited to people with schizophrenia but also occur in other diagnostic groups and independently of psychotic symptoms (e.g., Parker, 2002; Kraus & Sheitman, 2005). Notwithstanding the difficulties associated with further study, this needs to be examined more closely in RCTs looking specifically at aggression and violent behaviour.

Clinical implications

- The goal of long-term treatment is to decrease the frequency and intensity of future episodes of agitation or aggression.
- The perceived clinical driver for the aggressive behaviour (such as being delusionally driven or related to impulsivity or comorbid personality disorder) might dictate which medication is chosen in the first instance.
- It is important to address the multifactorial aetiology of violent behaviour, including any comorbid issues and environmental factors that contribute to increased risk.
- There is no justification in the published literature for high-dose antipsychotics in the treatment of persistent aggression. Regular and frequent review of treatment plans in relevant clinical settings might allow for the safe and appropriate use of antipsychotic medication without any increase in violence (Herlihy & Smith, 2010; Choong et al., 2011).
- When prescribing medication to target the medium- or long-term risk of violence, the clinician should bear in mind the limited evidence and only prescribe medication after a thorough multidisciplinary assessment, risk-benefit evaluation and careful review of effects and side-effects.
- Continuing adherence to prescribed medication is especially important in the long-term reduction of aggressive behaviour (Swanson et al., 2004, 2008; Arango et al., 2006).
- Of the available antipsychotic medications, clozapine has the best evidence base for reducing the risk of violence in people with schizophrenia in the long term. This treatment might have a specific effect on symptoms related to aggression.

Schizophrenia failing to respond to standard antipsychotic regimens

A series of controlled studies conducted between 1970 and 1980 compared very high doses of first-generation antipsychotics with standard-dose regimens for treatment-refractory schizophrenia. All failed to show a significant advantage for ‘mega’ dosages (Hirsch & Barnes, 1994; Thompson, 1994). Reviewing relevant data from RCTs of first-generation antipsychotics, Baldessarini and colleagues (1988) concluded that a dose–benefit relationship for antipsychotic drug treatment was probably to be found at a daily equivalent of between 100 and 700 mg of chlorpromazine. Higher doses were countertherapeutic, in that they were unlikely to be more effective but might well yield inferior average benefits as well as an increased risk of side-effects such as excessive sedation, EPS and iatrogenic negative symptoms (Wilkie et al., 2001). A similar conclusion was reached by Bollini et al (1994), who conducted a meta-analysis of 22 published RCTs comparing antipsychotic dosages and found ‘No incremental clinical improvement at doses above 375 mg equivalent of chlorpromazine, while a significant increase in adverse reactions was observed’. For first-generation antipsychotics, the 2009 PORT guidelines (Kreyenbuhl et al., 2010) recommend a dosage of 300–1000 mg chlorpromazine equivalents daily for acute exacerbations and, as already noted above, 300–600 mg chlorpromazine equivalents for maintenance doses.

Using RCT data, Davis & Chen (2004) calculated dose–response curves for individual antipsychotic drugs. This allowed them to identify the near-maximal effective dose for each drug, defined as the threshold dose necessary for all or almost all clinical response. For most antipsychotics, both first- and second-generation drugs, this near-maximal effective dose was less than the maximum licensed dose. Gardner et al (2010) found a strong correlation between these near-maximal effective doses and equivalent doses for antipsychotic drugs reached through a Delphi consensus method. Davis & Chen (2004) interpreted their data as a lack of evidence for greater efficacy with doses higher than the near-maximal effective dose, either generally or in any sub-populations, such as treatment-resistant psychotic illness.

A more up-to-date and sophisticated analysis on near maximal therapeutic doses across multiple antipsychotics generally supports this conclusion (Leucht et al., 2020). In addition, this pooled analysis of antipsychotic medications found a near maximal effective dose, expressed as a risperidone equivalent dose, of 13mg/day. The analysis also showed that for most antipsychotic medications the dose-response curve approaches a plateau beyond which there is little additional gain for dose increases. Moreover, for some drugs, such as risperidone and aripiprazole, there was a bell-shaped dose-response curve, indicating lower response on average at higher doses even within the licensed therapeutic range. Overall, these analyses show that for most drugs there is little further benefit from increasing the dose above the licensed therapeutic range, and for some drugs there may even be lower efficacy. However, for one or two drugs, notably olanzapine,

where there was no clear plateau in the dose-response curve, there may be some additional benefit from higher dose. Although this additional benefit is small, it may be clinically relevant in some patients, but must be weighed against the increased risk of side-effects (see section on side-effects).

There is a long-standing notion that doses of olanzapine above the licensed maximum (>20 mg a day) may be beneficial for treatment-resistant schizophrenia (see Sheitman et al., 1997; Mountjoy et al., 1999). Citrome and Kantrowitz (Expert Review of Neurotherapeutics 2009;9) commented that high-dose olanzapine may be helpful in TRS characterised by severe, persistent symptoms and/or acute agitation, but there was a need to balance against increased risk of metabolic side effects. In their meta-analysis of RCTs comparing olanzapine and clozapine for TRS, Souza et al (2013) found a trend toward high doses of olanzapine producing higher effect sizes for this drug. They concluded that 'the most robust evidence for efficacy in TRS supports clozapine, but olanzapine, particularly in higher dosage, is a treatment option to be considered'.

The Canadian Agency for Drugs and Technologies in Health's Optimal Use Report (2011) considered the value of high-dose second-generation antipsychotics versus standard-dose non-clozapine antipsychotics for treatment-resistant schizophrenia. They identified two relevant studies, one comparing high- with standard-dose quetiapine treatment in patients with persistent symptoms of schizophrenia (Honer et al., 2012) and another comparing high-dose risperidone with standard- dose haloperidol in a sample of in-patients with established schizophrenia (Claus et al., 1992). Meta-analyses detected no significant differences, although Positive and Negative Syndrome Scale (PANSS)-total and PANSS-positive scores were significantly improved with high-dose risperidone compared with haloperidol in the latter study. On the basis of this limited evidence, the Optimal Use Report recommended that high doses of a (non- clozapine) second-generation antipsychotic agent 'not be used instead of standard doses in patients with schizophrenia who inadequately respond to a standard-dose antipsychotic agent.'

If high dosage was effective for schizophrenia that had proved to be unresponsive to standard antipsychotic dosage, then a decrease in dosage might be expected to be associated with deterioration of illness and increased risk of relapse. But open studies suggest that many patients receiving a high dose of antipsychotic are potential candidates for successful dose reduction (Leblanc et al., 1994; Suzuki et al., 2003). This is also a possible interpretation of the results of a double-blind trial (Volavka et al., 2000) in a small sample of patients with schizophrenia receiving high-dose haloperidol (drug plasma level of 15 ng/ ml or higher). They were randomly assigned to either dose maintenance or dose reduction (to a target drug plasma level of 10 ng/ml). Both treatment groups showed an average, slight symptom reduction, but there were no significant differences between them.

Thus, despite considerable evidence for the effectiveness of antipsychotic drugs in the treatment of psychosis, there seems to be no good quality evidence that increasing the antipsychotic dose for illness not responding to initial antipsychotic treatment differs from continuing antipsychotic treatment at the same dose (Samara et al., 2018) or that use of high-dosage antipsychotic medication is more effective than standard dose, although a higher dose of olanzapine could be considered for TRS if clozapine has been ineffective or had to be stopped.

The original high-dose consensus statement (Royal College of Psychiatrists, 2006) recommended that, before resorting to a high-dose trial, other strategies with better evidence of efficacy, including clozapine treatment, should be tested. If high-dose antipsychotic medication is to be initiated, this should be as a limited, individual trial, with regular review of response and appropriate monitoring in relation to potential adverse effects and physical health. If no appreciable improvement has occurred after 3 months, there should be a return to standard dosage. In clinical practice, many people with illness that has proved refractory to standard treatment will be prescribed progressive increments in antipsychotic dosage over time but without documented monitoring of outcome, so that it might be difficult, in retrospect, to determine whether there was any associated benefit.

Clinical implications

- Treatment-resistant schizophrenia is usually defined as illness that has shown an insufficient response to adequate trials, in terms of dose, duration and adherence, of at least two different antipsychotic medications. NICE (2014) guidelines indicate that at least one of the drugs should be a non-clozapine, second-generation antipsychotic.
- There is no convincing evidence that antipsychotic dosage higher than the maximum licensed dose is more effective than standard dosage for treatment-resistant schizophrenia.
- Before resorting to high dosage, evidence-based strategies for treatment-resistant illness should be exhausted, including optimised use of clozapine.
- If a clinician initiates a high-dose antipsychotic treatment regimen, this should be as a limited therapeutic trial, with dosage returned to conventional levels after a 3-month period unless the clinical benefits evidently outweigh the risks.
- The potential side-effects of high-dose antipsychotic regimens should be monitored appropriately, by systematic enquiry, physical examination, ECG and appropriate haematological investigations.

Dose-related side-effects

Background

While it might be self-evident that the likelihood and intensity of most unwanted effects from antipsychotic medication increase with dosage, it is, perhaps, less well appreciated that the risk also rises with the speed of drug delivery/ dosage increase. However, some reactions are unpredictable in these terms and might reflect individual patient susceptibilities and have therefore been called idiosyncratic. Some reactions are neither clearly idiosyncratic nor dose related. This section considers reactions that are either clearly or possibly dose related, although it must be acknowledged that several factors potentially confound dose–response relationships, including the pharmacokinetics of the drug, the role of metabolites, and clinical characteristics of the individual patient. Nevertheless, appreciation of such relationships is crucial for an informed risk–benefit evaluation of antipsychotic agents, and this is especially true for the first-generation antipsychotics, which were licensed many years ago when, arguably, their risks and benefits were the subject of much less intense scrutiny. Despite assessments by the licensing authorities, their licensed dose ranges tend to remain relatively liberal and only loosely based on evidence. Certain members of the second-generation of antipsychotics (such as olanzapine and aripiprazole) have licensed dose ranges that are relatively narrow, which in itself might reduce the burden of clearly dose-related adverse effects.

Barnes and McPhillips (1999) reviewed the unwanted effects of second-generation antipsychotics: dose-related effects seen within the licensed dosage range include EPS (Parkinsonism, akathisia, acute dystonias, tardive dyskinesia), tachycardia, postural hypotension, sedation, seizures and hyperprolactinaemia. However, it must be emphasised that there is still a lack of robust data on the relative risk of these various adverse effects between the second-generation agents within the licensed dosage range (Pope et al., 2010), never mind at high dosage. Further, the risk of all these potential adverse effects need to be balanced against the significant potential health gain of receiving effective treatment.

Safety and tolerability

The relationship between the extent of antagonist action at D receptors and EPS translates clinically into a dose-related risk of EPS (see next chapter). Such a relationship can be seen for first-generation antipsychotics within the licensed dosage range (Leucht et al., 2009; Stone et al., 2009) and is likely with most second-generation antipsychotics when the licensed maximum dose is exceeded.

Hyperprolactinaemia is the result of antagonist action at D₂ receptors located on pituitary lactotrophs, and although roughly dose-related, it can occur with many antipsychotics at even low doses (Haddad & Wieck, 2004). Drugs with a relatively low risk of causing hyperprolactinaemia are aripiprazole, clozapine, olanzapine and quetiapine (Leucht et al., 2013). In addition to the well-documented effects of hyperprolactinaemia on sexual function (Baggaley, 2008), breast growth and galactorrhoea, there are potentially serious,

long-term, disabling consequences of high prolactin levels, such as osteoporosis. Osteoporosis is compromised bone strength, rendering it fragile and susceptible to fracture. There is a loss of mineral density, mainly calcium, as well as architectural loss of normal bone structure (Abraham et al., 2003; Meaney & O'Keane, 2003; Meaney et al., 2004). An association between persistently raised prolactin levels and the development of breast cancer (Harvey et al., 2008, Taipale et al., 2021) and prolactinoma (Akkaya et al., 2008) has been suggested but remains unproven.

Sedation is clearly dose-related and thought to reflect blockade of central histamine and/or alpha1 noradrenergic receptors. Some troublesome peripheral autonomic effects, such as dry mouth, constipation, urine retention and tachycardia, are generally related to anti-muscarinic action. Antipsychotic drugs vary in their capacity to block muscarinic acetylcholine receptors and thus their liability for these antimuscarinic/anticholinergic side-effects (Ozbilen & Adams, 2009). Antipsychotic drugs with relatively high intrinsic anticholinergic action, such as thioridazine and clozapine, might be expected to generate more of these problems (Chengappa et al., 2000). In one small study, high-dose quetiapine (although it has little if any affinity for cholinergic receptors) was associated with constipation in 42% and dry mouth in 25% of patients (Boggs et al., 2008), and there has also been a report of bladder distension associated with rapid loading of this drug (Chae, 2010). High-dose antipsychotics have been reported to cause paralytic ileus (Kwiatkowski et al., 2011). Central anticholinergic effects associated with antipsychotic treatment include cognitive impairment (Zachariah et al., 2002; Vinogradov et al., 2009), and a small study has shown that when very high doses of antipsychotic were reduced to high/standard dose, improvements were seen across a range of cognitive functions (Kawai et al., 2006). Clozapine might cause paradoxical hypersalivation partly through a complicated action at cholinergic receptors on salivary glands (Davydov & Botts, 2000).

All antipsychotics seem prone to causing weight gain to some extent (Allison & Casey, 2001; Bobes et al., 2003; McIntyre et al., 2003; Rummel-Kluge et al., 2010; Stroup et al., 2011; Leucht et al., 2013). There is marked individual variation in susceptibility to weight gain, so a drug might cause marked weight gain in one person but little or no weight gain in another (Bushe et al., 2012), presumably reflecting the importance of genetic susceptibility (Reynolds, 2012). For example, an association has been reported between common variants near the melanocortin 4 receptor gene and severe antipsychotic-induced weight gain (Malhotra et al., 2012). Antipsychotic-naïve patients are more prone to weight gain than chronic patients, although this might simply reflect a plateau effect. Affinity for 5-HT_{2C}, H₁, and alpha-2 adrenergic receptors, and effects on leptin and ghrelin, are all likely to be relevant (Rege, 2008). Although weight gain can occur with any dose, there is some suggestion that with olanzapine, at least, high doses are associated with greater weight gain than standard doses (Lieberman et al., 2005; Meltzer et al., 2008; Citrome et al., 2009; Simon et al., 2009). Combined antipsychotics, which are the main cause of high dosage (Paton et al., 2008), have been associated with an increased risk of obesity (Correll et al., 2007). 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 reduce life expectancy (American Diabetes Association et al., 2004; Rummel-Kluge et al., 2010; Thornicroft, 2011).

The incidence of unprovoked seizures in the placebo arms of RCTs of antipsychotic drugs is approximately 15-fold higher than the rate seen in the general population,

suggesting that psychosis itself is a risk factor for seizures (Alper et al., 2007). Among the first-generation antipsychotics, the risk of seizures seems highest with chlorpromazine. Several studies have confirmed that seizure risk is dose related with phenothiazines (Logothetis, 1967; Messing et al., 1984). Rapid increases in dose and the presence of organic brain disease also increase the risk of seizures. Among the second-generation antipsychotics, the risk of seizures is greatest with clozapine (Pisani et al., 2002). Once again, the risk increases with higher dose and rapid dose escalation. With clozapine, the risk of seizures is estimated at approximately 1% with doses below 300 mg/day and 4.4% with doses above 600 mg/day (Devinsky et al., 1991). Of the other second-generation drugs, zotepine (discontinued in the UK in 2011) has been reported to carry a relatively high risk of seizures (Hori et al., 1992). It might be safe to assume that any antipsychotic might lower the seizure threshold, and it has been suggested that antipsychotics with relatively potent antagonistic effects at histamine, serotonergic and noradrenergic receptors might be more liable to cause seizures (McConnell et al., 1997).

Extrapyramidal side-effects

EPS induced by antipsychotics are of critical clinical importance, not least because they have been shown to affect patients' quality of life negatively (Browne et al., 1996; Hofer et al., 2004; Adrianzén et al., 2010). These motor phenomena can be disabling and stigmatising, depending on their nature and severity. EPS can discourage adherence to the antipsychotic medication regimen because of how unpleasant they are for the patient. For example, drug-related Parkinsonism can leave those affected feeling dysphoric, apathetic, emotionally withdrawn and cognitively slowed (Tandon & Jibson, 2002), and akathisia is associated with feelings of restlessness, inner tension and mental unease (Barnes & Braude, 1985) and possibly a greater likelihood of suicidal ideation (Seemüller et al., 2012). EPS can also confound the clinical assessment of psychotic illness (Barnes & McPhillips, 1999). For example, akathisia is not uncommonly misdiagnosed as anxiety and agitation or psychotic exacerbation, which could prompt an increase in the dose of a patient's medication (Michaels & Mumford, 1989), and the features of Parkinsonism (particularly bradykinesia) show some phenomenological overlap with negative symptoms.

It is well established that acute EPS are more common with high-dose antipsychotic medication (Aubree & Lader, 1980; Li et al., 2009; Liu & De Haan, 2009). This is in line with the finding that acute EPS are associated with a striatal D2 occupancy beyond about 80% (Kapur et al., 2000; Tort et al., 2006). The risk of akathisia specifically has been shown to be greater with rapid escalation of antipsychotic dosage (Barnes, 1992). A key advantage claimed for second-generation antipsychotics is a lower liability for both acute and later onset EPS. However, individual second-generation antipsychotics differ in their propensity to cause EPS (Rummel-Kluge et al., 2012): for some (such as clozapine and quetiapine), acute EPS liability does not differ from placebo across their full dose, while for others, the risk is dose-dependent. These differences might reflect individual drug profiles in relation to properties such as D2-receptor affinity, speed of dissociation from the D2 receptor, antimuscarinic action, 5-HT_{2A} antagonism (for aripiprazole) partial agonism at D2 and 5-HT_{1A} receptors. Age-related reductions in risperidone clearance can increase this risk of EPS; Reeves et al., (2021) argue that the maximum prescribed dose should be lower for those of greater age with cognitive impairment.

Interpretation of the RCT evidence for the superiority of second-generation antipsychotics in respect of acute EPS needs to take account of the dosage and choice of first-generation antipsychotic comparator. This comparator is most often haloperidol, a high-potency D2 antagonist with a relatively high liability for EPS. Generally, studies in patients with schizophrenia and related disorders have found that second-generation antipsychotic drugs induce fewer EPS than haloperidol, even at low doses (Leucht et al., 2009). But the evidence for a lower risk of Parkinsonism and akathisia with second-generation antipsychotics compared with 'low-potency' first-generation antipsychotics is less than convincing, although patients receiving the second-generation drugs consistently seem to be less likely to be prescribed anticholinergic drugs (Leucht et al., 2003b; Peluso et al., 2012).

Current evidence also generally supports a lower risk of tardive dyskinesia with second-generation antipsychotics compared with first-generation antipsychotics (although, again, haloperidol was a common comparator in trials, used in relatively high doses) (Correll et al., 2004; Correll & Schenk, 2008). This might explain the tentative evidence of a decline in the incidence and persistence of tardive dyskinesia in routine clinical practice (Margolese et al., 2005). The incidence of tardive dyskinesia with clozapine seems to be substantially lower than with first-generation drugs, although episodes of dyskinesia and dystonia are occasionally seen on abrupt discontinuation (Ahmed et al., 1998). Some limited data suggest that switching to clozapine can exert a favourable effect on tardive dyskinesia in a proportion of cases (van Harten & Tenback, 2011). However, RCTs do not support the effectiveness of switching to other antipsychotics, including clozapine, as a means of influencing the course of the condition. Tardive dyskinesia, Parkinsonism and akathisia remain major problems, despite the widespread use of second-generation antipsychotics (Mentzel et al., 2017, Carbon et al., 2017, Shirzadi & Ghaemi, 2006; Kane et al., 2010; Peluso et al., 2012; Rummel-Kluge et al., 2012, Lerner et al 2015).

Neuroleptic malignant syndrome

Clinical features and pathophysiology

Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening idiosyncratic reaction to certain psychiatric drugs, most commonly antipsychotics. The cardinal features are muscle rigidity, pyrexia, altered consciousness and autonomic disturbance. The relationship between NMS and antipsychotic drug variables is uncertain. The syndrome is not clearly dose-dependent, but high dosage, rapid introduction or escalation of the dosage, and use of intramuscular agents might all be risk factors (Keck et al., 1989; Caroff & Mann, 1993; Berardi et al., 1998; Viejo et al., 2003; Langan et al., 2012). Most cases appear within a week of starting a new antipsychotic, particularly if the dose has been rapidly increased, but NMS can also occur during long-term antipsychotic treatment on a stable dose (Pope et al., 1991). The syndrome is particularly associated with the use of high-potency, first-generation antipsychotic drugs such as haloperidol, but cases have been reported with second-generation antipsychotics including amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine and risperidone (Bottlender et al., 2002; Ananth et al., 2004; Chakraborty & Johnston, 2004; Nayak et al., 2011; Su et al., 2014). Non-antipsychotic drugs occasionally associated with NMS include lithium, antidepressants and metoclopramide (Haddad, 1994). The syndrome can also follow the sudden withdrawal of dopamine agonists in Parkinson's disease (Man, 2011; Wu et al., 2011) and has been reported as a rare complication of deep brain stimulation (Boviatsis et al., 2010).

NMS is more common in men than women. Most cases occur in adults under 40 years of age (Caroff, 1980) but the syndrome has been reported in children (Abu-Kishk et al., 2004) and in elderly patients with dementia (Warwick et al., 2008) who have been treated with antipsychotic drugs. Caroff and Mann (1993) reported an incidence of 0.2%, but the incidence seems to have decreased in the decades since. A Danish case-register study covering an 11-year period (1996 to 2007) suggested an occurrence of 0.04%: 83 patients with NMS among nearly a quarter of a million patients with psychiatric illness (Nielsen et al., 2012). The falling incidence might reflect better prescribing, with less frequent use of antipsychotic polypharmacy, the use of lower antipsychotic doses and the introduction of the second-generation antipsychotics, although tighter diagnostic criteria might also have contributed to the decrease.

There are many secondary medical complications associated with NMS, including myoglobinuria, renal failure, respiratory failure, aspiration pneumonia, seizures, disseminated intravascular coagulation and multi-organ failure. The associated mortality has decreased in recent decades (Shalev et al., 1989; Caroff & Mann, 1993), perhaps reflecting better recognition, diagnosis and management. In an analysis of NMS cases reported to the Australian Adverse Drug Reaction Advisory Committee between April 1994 and September 2010, mortality was lower for cases associated with

second-generation antipsychotics than those related to first-generation drugs (3.0% v. 16.3%; Trollor et al., 2012).

Symptoms typically evolve over several days and can fluctuate. NMS occurs on a spectrum of severity. In severe cases, patients are mute and akinetic, have generalised 'lead pipe' muscle rigidity and marked hyperthermia (temperature up to 42 °C), but the diagnosis of milder or partial forms of the syndrome is less obvious. Rigidity is less common in cases associated with clozapine than in cases associated with first-generation antipsychotics (Trollor et al., 2012). There are no pathognomonic investigations, though serum creatine phosphokinase is nearly always elevated (often markedly so), reflecting sustained muscle contraction and necrosis, and leukocytosis is frequent.

NMS is believed to be due to a sudden and marked drop in dopamine transmission. Usually this will be caused by a newly commenced and potent antipsychotic blocking central dopamine receptors. However, this model also explains how the sudden withdrawal of a dopamine agonist in Parkinson's disease can sometimes precipitate NMS (Man, 2011; Wu et al., 2011). Reduced dopamine transmission in different pathways might account for different features of NMS. According to this model, reduced dopaminergic transmission in the thermoregulatory centre of the anterior hypothalamus causes pyrexia, in the striatum it is associated with muscle rigidity, in the nigrostriatal and mesocortical systems it leads to mental state changes, and reduced dopamine transmission in the spinal cord might cause the autonomic features. Muscle rigidity causes peripheral heat production, thereby contributing to pyrexia. A syndrome virtually identical to NMS, termed lethal catatonia, was reported by Kahlbaum in the pre-antipsychotic era (Weller, 1992; White, 1992).

Management

If NMS is suspected, antipsychotic medication should be stopped, as should other dopamine antagonists (e.g., metoclopramide) and other potentially causative drugs (e.g., antidepressants and lithium). If the syndrome has followed cessation of dopaminergic therapy in patients with Parkinson's disease, the medication should be restarted. An urgent medical opinion should be obtained. Transfer to a medical bed will be required if more specialised treatment is needed. General supportive measures should be instigated, including rehydration, cooling and the treatment of any intercurrent infection. Secondary complications, such as hypoxia, acidosis, and renal failure, require aggressive treatment. Specific therapies to treat NMS, in addition to supportive measures, include prescribing dopamine agonists (bromocriptine, amantadine), benzodiazepines (Susman, 2001) and the muscle relaxant dantrolene (Susman, 2001; Reulbach et al., 2007) to facilitate muscle relaxation. The decision on whether to adopt these approaches should be made by a physician.

NMS is not an absolute contraindication to further antipsychotic treatment, although clearly if the underlying psychiatric condition can be treated without antipsychotic medication, this option should be considered. For example, if NMS has occurred during the treatment of mania with an antipsychotic, consideration should be given to treating the mania with an appropriate mood stabiliser instead. Estimates of the risk of recurrence of NMS following re-challenge with antipsychotic medication vary. Two small case series

suggest that at least half of all patients who have experienced an episode of NMS are eventually able to be treated successfully with antipsychotics again (Rosebush et al., 1989; Olmsted, 1998). A minimum 2-week, antipsychotic wash-out period between resolution of NMS and restarting antipsychotic treatment seems to reduce the risk of recurrence (Rosebush et al., 1989). A different antipsychotic to that implicated in the original episode of NMS should be chosen and ideally it should be a low dose of a low-potency agent. Depot antipsychotics should not be used, as their sustained release from the depot injection site means the antipsychotic cannot be rapidly withdrawn if NMS reappears. Close monitoring is required if antipsychotics are restarted, to help identify the early reappearance of NMS. This includes monitoring for pyrexia, autonomic instability, changes in mental state, and rigidity, and taking serial measurements of the white cell count and serum creatine phosphokinase.

Cardiac side-effects of antipsychotics

Relationship to dose

A link between antipsychotics and ventricular arrhythmias and sudden death was made soon after their clinical use became widespread. A nationwide case cross-over study on antipsychotic medication and the risk of Ventricular Arrhythmia (VA) and/or Sudden Cardiac Death (SCD) found that antipsychotic use was associated with a 1.53-fold increased risk of VA/SCD, after adjusting for time-varying confounding factors. Risk of VA/SCD among FGA users might be higher than that among SGA users. Antipsychotic medications with an increased risk of VA/SCD included haloperidol, prochlorperazine, sulpiride, thioridazine, quetiapine, and risperidone (Wu C et al., 2015). However, pharmacoepidemiological studies have shown that all-cause mortality is lower in patients taking low or moderate dosage antipsychotics relative to not taking antipsychotics (Tiihonen et al., 2016). Moreover, the mortality from cardiac disease is not increased, and may even be decreased for some drugs, in patients taking antipsychotics relative to those not taking antipsychotics (Taipale et al., 2020). These findings indicate that overall, there is a clear benefit from antipsychotic treatment, but they do not preclude a risk from high dose treatment at the individual level. We therefore face the challenge of balancing the unknown but rare risks of serious adverse reactions against the undoubted benefits of treatment. This chapter attempts to identify the key risk factors for cardiac complications and suggests strategies to minimise their occurrence.

The primary mechanism of the cardiac complications of antipsychotics is thought to be abnormal cardiac repolarisation, which is mediated by the drugs binding to cardiac potassium channels (IKr) and resulting in blockade of potassium efflux from the cardiomyocytes. This is an entirely separate mechanism from their primary pharmacological action and therefore the risk of arrhythmia is not associated with any clinical advantage. Many antipsychotics prolong ventricular repolarisation, potentially giving rise to a prolonged QT interval on the ECG (O'Brien & Oyebode, 2003) and to the characteristic polymorphic ventricular tachycardia termed torsade de pointes (TdP). TdP typically manifests as convulsions, dizziness and syncope, but it can also lead to ventricular fibrillation and sudden cardiac death.

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 correction for heart rate) as a more appropriate measure. There are problems in reliably measuring QTc (especially when the heart rate is over 100 beats per minute, as can be found in patients receiving antipsychotic medication) and there is only weak consensus on the cut-off points for abnormality (Gupta et al., 2007). Nevertheless, there is general agreement that QTc intervals longer than 500 ms are a major risk factor for TdP. Other indicators of abnormal repolarisation include abnormalities of the T-wave or large U-waves.

Risk factors for QTc prolongation and associated arrhythmias

QT-interval prolongation might be congenital or acquired. Congenital long QT syndrome is rare, and results from mutations of genes encoding cardiac ion channels (particularly the potassium channel IKr). Patients who have abnormal ventricular repolarisation are at increased risk of developing arrhythmia when started on drugs that prolong repolarisation. Patients who have had previous episodes of TdP are at particular risk, even if a different drug had previously provoked it. Patients with pre-existing cardiac disease such as left ventricular dysfunction or hypertrophy are also at increased risk. Age might be an independent risk factor. TdP is most likely to occur when the heart rate is slow and in the presence of extrasystoles. Thus, conditions associated with these phenomena, such as heart block, increase the risk of TdP. Arrhythmia is more likely to occur in the presence of electrolyte abnormalities, for example hypokalaemia, hypocalcaemia or hypomagnesaemia. Treatment with diuretics seems to increase the risk, probably by producing such electrolyte abnormalities. Patients who are malnourished and those with alcohol dependence might 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 TdP occur in women (Makkar et al., 1993). There is evidence that TdP most often occurs early in therapy, which has implications for monitoring, as it is logical to focus on monitoring at the time of highest risk.

Antipsychotics and the risk of arrhythmia and sudden death

Some antipsychotic drugs are more potent than others at producing QT-interval prolongation and arrhythmia at therapeutic doses (Wenzel-Seifert et al., 2011). Initially, there were case reports and case series of arrhythmia and sudden unexpected deaths with antipsychotics that highlighted the risk of higher doses. Reports of 13 sudden deaths in patients receiving pimozide prompted the UK Committee on Safety of Medicines (1990) to issue specific recommendations for this drug, which include gradual dose escalation and the recording of an ECG before, and periodically during, treatment in those receiving high doses. Haloperidol has no clear effect on QTc at low or at moderate daily doses but has been associated with cases of QTc prolongation and TdP 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 (Hassaballa & Balk, 2003; FDA, 2007). 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 100 mg daily or more caused QT-interval abnormalities in over half of recipients (Buckley et al., 1995). Thioridazine-induced QT prolongation is linked to thioridazine plasma concentration (Hartigan-Go et al., 1996; Thanacoody et al., 2007). A study in Finland

of 49 cases of sudden death in patients taking psychiatric drugs found that 46 were exposed to a phenothiazine; this was thioridazine in 28 cases, a figure that was out of proportion to the local use of the drug (Mehtonen et al., 1991).

These case series prompted a number of controlled studies that have clarified 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 a prolonged QTc (defined as >420 ms) was more common in treated patients than in controls, particularly in those taking high doses (more than 2000 mg 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 1000 mg chlorpromazine equivalents) or very high (over 2000 mg chlorpromazine equivalents) doses were used, compared with lower doses.

Similarly, epidemiological studies have identified risks for cardiac death related to antipsychotic use and have highlighted the important role of high dose in this effect (Osborn et al., 2007; Correll et al., 2017). Ray and colleagues (2001) investigated the rate 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 group not exposed to antipsychotics. This figure increased to 14.4 and 26.9 deaths 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 five psychiatric hospitals over a 12-year period. Most of the deaths were of elderly patients (median age 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. Straus et al (2004) performed a population-based case–control study of 554 cases of sudden cardiac death in the Netherlands. They showed that the risk of death was three times higher in those receiving antipsychotics and the association was related to both dose and duration of treatment. Waddington and co-workers (1998) linked antipsychotic polypharmacy with excess mortality in schizophrenia. Tiihonen and colleagues (2012) have recently shown an association between concomitant benzodiazepine use and increased mortality in schizophrenia. A recent study of sudden death in psychiatric in-patients in England and Wales (Windfuhr et al., 2011) confirmed benzodiazepine usage, use of two or more antipsychotics, clozapine, and cardiovascular, respiratory and dementing diseases as independent risk factors for sudden, unexplained death in this population.

Concern about the risk of QTc prolongation and arrhythmias resulted in regulatory changes in 2002 that restricted the indications for thioridazine in both the UK and USA. The manufacturers of droperidol suspended marketing of this product. (Note: thiothixene has never been licensed in the UK.)

Most of the epidemiological studies described above were conducted before the introduction of second-generation antipsychotic drugs. This section reviews the available evidence on the cardiac safety of these drugs. There seem to be only small effects at low doses, but at higher doses there are modest effects on QTc for the majority of the commonly used second-generation antipsychotics (Harrigan et al., 2004) but no drug was associated with a mean QTc of greater than 500ms. The dose effect is better established for clozapine (Kang et al., 2000) and is seen following overdose. The second-generation antipsychotic sertindole was linked with QT-interval prolongation with 36 suspected adverse drug reactions with a fatal outcome (though not all of these related to sudden cardiac death) 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 (see 'Clinical implications' section). More recently, Thomas et al (2010) showed in a multinational, open-label RCT in schizophrenia that sertindole was associated with a small but significant increase in cardiac mortality. The frequency of QTc prolongation with ziprasidone has been reported at 0.06% (Trenton et al., 2003); the drug currently does not have a UK licence. However, in the USA, where the drug is licensed, the recent ZODIAC study, comparing 1-year mortality rates associated with ziprasidone and olanzapine in real-world use, found no differences between them (Strom et al., 2011).

The frequency of TdP in patients on second-generation antipsychotics has not been studied in controlled trials, but in data from the FDA Adverse Event Reporting System from 2004 to 2007, a small number of cases were reported for ziprasidone, haloperidol, risperidone and quetiapine, but not for olanzapine (Poluzzi et al., 2009).

Because of the relatively low rates of QTc prolongation and TdP with second-generation antipsychotics, it was thought these drugs had better cardiac safety than the older antipsychotics. However, in 2009, Ray and colleagues showed that current users of second-generation antipsychotics in a large cohort of adults had a dose-dependent increase in the risk of sudden cardiac death that was identical to that of users of first-generation agents, even when cardiovascular disease variables were controlled for. Both this study and another by Karlsson et al (2009), which examined the WHO drug safety database (VigiBase), showed that the risk of sudden death with second-generation drugs persisted when the analysis excluded long-term users, suggesting that acute drug effects are involved. The mechanisms whereby such antipsychotics are associated with sudden death are unknown but might be related to factors other than their relatively weak effects on cardiac repolarization, including autonomic effects, inhibition of other ion channels or some form of cardiotoxicity, perhaps mediated by their metabolic effects.

Clinical practice guidelines by Lambiase et al (2019), suggests the overall and cardiovascular mortality distributions follow a U-shaped curve in relation to antipsychotic dose with patients taking no medication and those taking the highest doses having the greatest mortality. This indicates that antipsychotics can protect patients against the consequences of schizophrenia, including suicide, at low and medium cumulative doses; compliance is critical and high doses should be avoided (Taipale et al., 2018).

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 TdP. As a result, some patients who do not express individual isoforms might 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

The most important pharmacodynamic interactions are from the combined use of two drugs that prolong ventricular repolarisation, since these might have an additive effect on the QT interval. A detailed account of these drugs can be found in a review by Taylor (2003), but in psychiatric prescribing practice, particular note should be taken of the potential QT-prolonging effects of some antidepressants, although the relative liability of antidepressants for QTc prolongation and ventricular arrhythmia remains uncertain (Medsafe, 2012; Zivin et al., 2013)

Pharmacokinetic drug interactions resulting in increased plasma or tissue concentrations of a QT-interval-prolonging drug are another important source of TdP. 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. It is important to note that some hepatic enzyme inhibitors (e.g., erythromycin, ketoconazole) also delay cardiac repolarisation in their own right, and this effect increases the severity of the interaction. In the context of prescribing in psychiatry, there is increasing evidence of significant interaction between antipsychotics and some selective serotonin reuptake inhibitors (e.g., paroxetine, fluoxetine, sertraline). A detailed account of important interactions between psychotropics can be found in 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 might 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; Windfuhr et al., 2011). However, the use of restraint and/or seclusion is infrequent in these studies, leading to uncertainty as to whether these factors increase the risk of sudden death in psychiatric patients and highlighting the need for further research. There is no evidence that current forms of rapid tranquillisation are associated with sudden death (Abdelmawla & Mitchell, 2006).

A Swedish nationwide study examined mortality risk between antidepressants and antipsychotics with various TdP risk in people above the age of 65 dying outside the hospital. These results suggest that the TdP risk with antipsychotics should be taken into consideration when prescribing for older people (Danielsson et al., 2015).

Drugs of abuse

The impact of recreational substances on cardiac repolarisation and sudden cardiac death is unclear (Royal College of Psychiatrists, 1997). There are few published data in this area and further research is needed. QT-interval prolongation has been reported with ecstasy and cocaine (Drake & Broadhurst, 1996; Pereira et al., 1997). Sympathomimetic agents might increase the risk of ventricular arrhythmia, independent of any effects on repolarisation. There is, however, good evidence that methadone prolongs the QTc in a dose-dependent manner, particularly when protein binding of the drug is low, as found in malnourished addicts or those with cirrhosis (George et al., 2008). Methadone was one of the drugs most commonly associated with TdP events reported to the FDA Adverse Event Reporting System (Poluzzi et al., 2009).

Clinical implications

- Most antipsychotic drugs are associated with a small but definite increase in the frequency of QTc prolongation, TdP and sudden cardiac death. These risks are heightened with higher doses and autonomic arousal, and in some patient groups (e.g., females, those with cardiovascular or liver disease, and those also taking other drugs with cardiac effects or risky pharmacokinetic interactions). Vigilance for these complications is required in all patients and investigation of patients with symptoms such as syncope is always warranted.
- Attention should be paid to the general health of patients with psychosis. Modifiable risk factors for ischaemic heart disease (e.g., smoking, hypertension, hyperlipidaemia, sedentary lifestyle) 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 with 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 might result in a drug interaction or additive ECG effects.
- All patients should be assessed for cardiovascular disease by means of history (e.g., chest pain, fainting, palpitations, diagnosed cardiac disease) prior to the institution of antipsychotic drug therapy, regardless of dose. Enquiry should be made about any family history of premature, sudden death. The presence of these or other factors, such as poor nutrition or liver disease, should influence the choice of antipsychotic drug, the starting dose and/or the increase in frequency of monitoring required, as well as prompt a more detailed cardiac assessment. This assessment should, whenever possible, include an ECG, which should be

examined for evidence of ischaemic heart disease, left ventricular hypertrophy and repolarisation abnormalities.

- Routine ECG is a key part of quality medical care, but as a means of identifying prolonged QTc it can be of uncertain value, and for assessing cardiovascular risk it is no substitute for a detailed family and personal history. That said, an ECG prior to, and ECG monitoring during, antipsychotic therapy is particularly important in the following situations:
 - high-risk antipsychotic drug treatment is contemplated (e.g., pimozide, haloperidol, sertindole)
 - high-dose or short-acting, parenteral antipsychotic drug therapy is to be used in an elderly patient or a patient with a history of cardiovascular disease. Urea and electrolytes should also be checked (particularly plasma potassium), especially in patients at higher risk of electrolyte abnormalities (e.g., patients with anorexia nervosa, liver disease, diuretic use or dehydration). ECGs should be performed every few days following initiation of high-dose treatment 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).
- In the circumstances of rapid tranquillisation where assessment of cardiovascular disease and status is difficult and carrying out an ECG is impossible, it is prudent to avoid high doses of antipsychotics, especially parenterally.

High-dose antipsychotics and cognition

Background

Cognitive impairment, present from illness onset, is widely accepted as a core feature of schizophrenia. Studies assessing antipsychotic medication effects on cognition initially seemed to show a beneficial effect for second- over first-generation drugs. When RCTs were subsequently undertaken, with first-generation drugs prescribed at doses equivalent to those of second-generation drugs, no particular advantage of one type of drug over the other emerged, although improvements in cognition were seen with both (Cuesta et al., 2001; Keefe et al., 2004; Veselinović et al., 2019). Longitudinal studies involving healthy controls have since suggested that the apparent improvement in cognition seen with antipsychotic drug treatment is likely to be due to non-specific practice effects (Goldberg et al., 2007; Guo et al., 2011).

On the basis of these studies, it can be concluded that standard doses of antipsychotic drugs do not have clinically relevant beneficial effects on cognitive function in schizophrenia. Further, given what is known about the role of dopamine in cognition, antipsychotics might be expected to have detrimental effects. Animal models show that dopamine neurotransmission mediates reward-dependent learning and is also critically involved in working memory. People with intrinsically reduced dopamine neurotransmission, for example in Parkinson's disease, show slowing of information-processing speed and impairments on tests of frontal-cortex function (e.g., working memory). These findings suggest that antidopaminergic drugs could negatively affect already compromised cognition function in people with schizophrenia, especially at higher doses. One study, the CATIE trial, examined the relationship between D2 occupancy levels, prescribed doses of antipsychotics, and cognition and found a nonlinear relationship between prescribed antipsychotic doses and poorer overall neurocognitive function and vigilance and that the D2 occupancy above approximately 80% increases the risk for cognitive impairment. (Sakurai H et al., 2013). Moreover, Oades et al (2000) used indirect measures of central dopamine-receptor occupancy in medicated patients and found that high occupancy was related to impaired verbal fluency but improved episodic memory. This study supports the view that high-dose antipsychotics can lead to impaired performance on tests of frontal-cortex function.

Effects on cognitive function

Evidence from two meta-analyses of antipsychotic dose effects on cognition gives direct support for the view that high dosage is detrimental to cognitive function. Woodward et al (2007) found a significant negative correlation between the effect size of medication on general cognition and haloperidol dose, but only if they included two 'outlier' studies that used more than 24 mg/day (equivalent to >1200 mg chlorpromazine). No relationship

was found for studies that used 2–15 mg/day. When individual tests were considered, there was a significant inverse correlation across all doses for verbal learning. Knowles et al (2010) examined processing speed, a form of cognition noted to be particularly impaired in schizophrenia, and found a significant negative relationship with dosage. The dose range was up to 900 mg/day chlorpromazine equivalents, suggesting that there would be an even stronger effect for doses over 1000 mg.

Studies specifically examining the effects of very high dosage on cognition are relatively rare. Several studies have directly compared groups of patients prescribed low and high doses of antipsychotic medication using the cut-off of 1000 mg chlorpromazine equivalents, while attempting to match for variables that might affect cognition, such as age, symptom severity, length of illness, number of relapses, and use of anticholinergic medication. The results are inconsistent. Kontis et al (2010) found no differences across a representative range of cognitive tests in groups matched for illness severity, baseline cognition and demographics. Hori et al (2006), on the other hand, found that a group receiving high dosage performed more poorly on measures of IQ and memory.

A different approach has been to examine the effect of dose reduction in patients being treated with very high doses. Kawai et al (2006) reduced first-generation antipsychotic medication dosage from 1400–3400 to 1000–1535 mg/day chlorpromazine equivalents in some patients and compared their changes in cognitive function with that of patients who remained on very high doses. Even though the medication-reduction patients were still taking doses considered to be high, they showed an improvement on a test of frontal cortical function, the Wisconsin Card Sorting Test, but no improvement on a test reflecting speed of information processing.

Yet another approach has been to examine subjective cognitive function. Moritz et al (2002) asked patients to rate their own mental functioning. Patients taking over 400 mg/day chlorpromazine equivalents of first-generation antipsychotic medication rated themselves significantly more impaired than those taking less, even when the analysis controlled for symptoms, whereas those taking high doses of second-generation drugs (i.e., >15 mg olanzapine or >6 mg risperidone) were not more adversely affected.

In summary, there is a lack of research concerning the effects of high doses of antipsychotics on cognition. The existing evidence, together with what is known about the role of dopamine in cognition, suggests that high doses of medication with potent dopamine-receptor-blocking action can cause cognitive impairment, particularly in frontal executive function.

Clinical implications

- Clinicians should be aware that prescribing high doses of antipsychotics might worsen already compromised cognitive function in their patients.
- High-dose antipsychotics have a greater liability for EPS, for which anticholinergic/anti-Parkinsonian agents might be required. This medication can negatively affect cognitive performance, particularly in older patients (Fox et al., 2011; Desmarais et al., 2012).

Potential gender and ethnicity factors and high-dose strategies

It is now clear that gender and ethnicity affect the efficacy and tolerability of some medicines, and 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. There are known differences in pharmacokinetics between men and women. For example, women produce less gastric acid than men, weigh less, have less total body water and a higher proportion of body fat, and clear renally and hepatically excreted drugs more slowly. The impact of these individual differences is complex to evaluate but they generally result in greater bioavailability and reduced elimination (Robinson, 2002) in ways that are clinically relevant. For example, the differences in volume of distribution and metabolic capacity between the genders explains the safe drinking limits for alcohol being set 50% higher for men than for women.

Pharmacokinetic considerations alone would suggest that the threshold for determining what is a high dose of antipsychotics for women should be scaled down, but there are no guidelines to say by precisely how much. Indeed, women tend to be under-represented in pre-licensing RCTs of antipsychotic drugs and tolerability data are generally not analysed or presented by gender.

The difference in population pharmacokinetic parameters between men and women is perhaps best illustrated with clozapine: women require a dose that is around 20% less than men require to achieve the same plasma clozapine level. The average male non-smoker requires 325 mg per day to achieve a plasma clozapine level of 350 ng/ml, whereas a female non-smoker requires only 265 mg (Rostami-Hodjegan et al., 2004). Where the patient is a smoker, the same proportional differential can be seen, with the average male smoker requiring 525 mg per day to achieve a plasma clozapine level of 350 ng/ml and the average female smoker requiring 435 mg. Similar findings for gender differences in drug plasma levels have been reported for olanzapine and risperidone (Patel et al., 2011; Bowskill et al., 2012a). These gender differences in dosage requirements seem to be applied in clinical practice. For example, in a benchmarking audit of clozapine use in UK mental health services, initiated in 2018, with data from 63 NHS Trusts/healthcare organisations and including 6948 patients prescribed clozapine POMH-UK (2020), the median dose of clozapine for women was 294 mg, whereas for men it was 324 mg.

The same POMH report reported findings from a 2017 audit of over 10,000 patients from acute clinical teams, rehabilitation teams and forensic teams, and regular high-dose antipsychotic medication was prescribed for 10% of patients overall, but only one third of these had high-dose prescription acknowledged in their care plan (POMH-UK 2020). This was reduced from a previous POMH dataset, when 433/1600 women (27%) were prescribed a high dose, compared with 820/2144 men (38%) (POMH-UK 2012). Here, for those who were prescribed a high dose, the median percentage maximum dose was 165% for women and 182% for men. Thus, in the UK, there is evidence to suggest that men are both more likely to be prescribed a high dose than women (using a categorical cut-off point) and more likely to receive a higher absolute dose overall. Other studies have found high-dose antipsychotic medication to be more commonly prescribed for men (Barbui et al., 2007; Paton et al., 2008) but this has not been an entirely consistent finding (Sim et al., 2009).

Another relevant question is whether there is a lower requirement for antipsychotic drugs in females because the oestrogen status of pre-menopausal women confers a higher sensitivity to dopamine-blocking drugs. This possibility has been reviewed by Salokangas (2004): 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. This paper discussed in detail the oestrogen-sensitisation hypothesis, but did not address simpler pharmacokinetic hypotheses, such as those described above. Hormonal transitions during the menstrual cycle might also influence drug response (Seeman, 2004). In addition, women are more likely to develop hyperprolactinaemia than men, and those who are of reproductive age and have previously given birth seem particularly vulnerable (Walters & Jones, 2008).

Clinical implication

- A broad conclusion is that women are likely to require lower doses than men, both overall and in high-dose scenarios.

Ethnicity

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

Clinicians might be concerned with whether higher doses are required for African and Afro-Caribbean patients, as there have been some reports that such patients might be prescribed higher doses of antipsychotics and more often receive depot preparations and first-generation antipsychotics than second-generation antipsychotics (Copeland et al., 2003; Kreyenbuhl et al., 2003). However, when potential confounders such as gender, being detained under the Mental Health Act, and having a forensic history or history of substance misuse are considered, Black patients are no more likely to be prescribed

high-dose antipsychotics than White patients (Connolly & Taylor, 2008; Paton et al., 2008; Connolly et al., 2010), at least in in-patient populations in the UK.

Generally, the wide variability in therapeutic response observed in individuals treated with psychotropic drugs suggests that this 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; Bondy & Spellmann, 2007). 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 (Bondy & Spellmann, 2007). 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 parent blood levels for a given dose of these drugs. There are ethnic differences in the distribution of such poor metabolisers (Reynolds et al., 2006; Bondy & Spellmann, 2007): for example, with CYP2D6, there is a lower incidence of poor metabolisers in the Asian population (1%) than in the White or African populations (5–10%). For antipsychotic drugs that are metabolised by CYP2D6 such as aripiprazole and risperidone, the risk of high antipsychotic drug levels should be lower in Asians.

Genetic polymorphisms involving genes that code for the synthesis, processing or degradation of neurotransmitters have been implicated in the aetiology of schizophrenia, but while some associations between these polymorphisms and response to newer antipsychotics have been shown, they are generally weak and do not as yet have clinical utility (Bondy & Spellmann, 2007; Haung et al., 2016).

Withdrawal of high-dose antipsychotics

Rationale

On the basis of the lack of evidence for efficacy of high doses of antipsychotics, as well as their known associated risks, dose reduction is probably an appropriate strategy for many patients on high doses. Similarly, if a patient has had a carefully considered trial of a high dose for a limited period of time, during which monitoring has found the high dose to be either ineffective or intolerable, dose reduction is also indicated.

Evidence

Evidence on how to withdraw or reduce high doses of antipsychotics is sparse. In studies conducting standard dose reduction (e.g., to examine the effect on adverse effects), the reduction method is usually step-wise over weeks and the magnitude of dose reduction is expressed as a percentage of the starting dose (e.g. 10% reduction weekly over 6–12 weeks). Current clinical guidelines lack detail on how to reduce or withdraw licensed doses of antipsychotics, presumably because this is usually done in the context of switching to another antipsychotic, in which case cross-tapering is generally recommended. Where more than one antipsychotic requires dose reduction, for example in a high-dose combination, one study suggests that the antipsychotic with the least relative potency should be decreased first (Suzuki et al., 2003).

Clinical implications

- Resistance by others, including members of the clinical team, to a reduction in dose might be due to concerns regarding the risk of the patient causing harm to self or others (Thomas et al., 1997). These concerns need to be balanced against the risk of harm to the patient's health by adverse effects of high doses and lack of clinical benefit
- In the absence of evidence, a gradual, step-wise dose reduction to the maximum licensed dose over a period of time, with monitoring for emergent adverse effects, would seem to be the most sensible strategy. A subsequent reduction to the minimum effective dose should also be considered.
- Ideally, other prescribing changes that were scheduled to occur at the same time should be minimised, in order to assist identification of the causal agent for any emergent adverse effects or clinical benefits.

Off-label use of a licensed medicine

'Off-label' medication use refers to the use of a licensed medicine outside the terms of the UK marketing authorisation (previously known as a product licence). This is different from the use of an unlicensed medicine (a product that does not hold a UK marketing authorisation for any indication). A good example of off-label usage is using higher than the maximum licensed dosage. In 2017, the Royal College of Psychiatrists produced guidance on 'Use of licensed medicines for unlicensed applications in psychiatric practice', which includes recommendations to clinicians regarding appropriate procedures when prescribing medication off-label (Royal College of Psychiatrists, 2017).

Relevant General Medical Council (2013) guidance states that when prescribing a medicine off-label you must:

- be satisfied that it would better serve the patient's needs than an appropriately licensed alternative
- be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy; the manufacturer's information might be of limited help, in which case the necessary information must be sought from other sources
- take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring and any follow-up treatment, or arrange for another doctor to do so
- make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing the medicine.

Certain off-label use is well established in clinical practice and widely supported in the medical literature. This includes, for example, the use of sodium valproate as an antimanic agent or mood stabiliser (only semisodium valproate is licensed for the treatment of acute mania and no valproate formulation is licensed for the maintenance treatment of bipolar disorder). Other off-label scenarios commonly encountered in psychiatry are the use of medicines outside the licensed age range (i.e., in adolescents and children or the elderly). In a review of off-label prescribing of antipsychotic medication, Haw and Stubbs (2007) concluded that it frequently lacks the support of robust clinical trials and that when prescribing off-label, the prescriber must carry out a careful risk assessment of the risks and benefits for the individual patient. They should also inform the patient that the prescription is off-label. The Medicines and Healthcare Products Regulatory Agency (2014) summarises best practice as listed below.

- Patients, or those authorising treatment on their behalf, should be given sufficient information about the proposed treatment, including known serious or common adverse reactions, to enable them to make an informed decision.

- Where current practice supports the use of a medicine outside the terms of its licence, it might not be necessary to draw attention to the licence when seeking consent. However, it is good practice to give as much information as patients or carers require or that they might see as relevant.
- You should explain the reasons for prescribing a medicine off-label or prescribing an unlicensed medicine where there is little evidence to support its use, or where the use of a medicine is innovative.

The responsibility that falls on healthcare professionals when prescribing an unlicensed medicine or a medicine off-label might be greater than when prescribing a licensed medicine within the terms of its licence. Using unlicensed medicines or licensed medicines outside the parameters of the marketing authorisation is not illegal, or necessarily inappropriate, and such prescribing practice is accommodated in the Medicines Act 1968. However, if a clinician prescribes a medication off-label, then he/she or his/her employers have increased liability. However, refusing to prescribe off-label might also have legal implications, as off-label prescribing indications are often described in standard textbooks as the treatment of choice.

Prescribers should therefore pay particular attention to the risks associated with using a licensed medicine off-label. These risks might include poor efficacy, adverse reactions, and discrepant product information or labelling (e.g., potential confusion for patients or carers when the Patient Information Leaflet is inconsistent with a medicine's off-label use). Attention is particularly important with high-dose antipsychotic medication, and the risks outlined in the relevant sections of this Report need careful consideration.

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