BNF 4.2

Monitoring unwanted effects of antipsychotics

Antipsychotic drugs are licensed as treatment for schizophrenia and other mental health disorders but can cause a range of unwanted effects that require close monitoring by, and close collaboration between, healthcare professionals across a range of settings. This applies to both first-generation and second-generation antipsychotics (FGAs and SGAs; sometimes known as conventional and atypical antipsychotics, respectively). Here we discuss monitoring for unwanted effects of antipsychotics in adults, with a particular focus on SGAs.

Background

FGAs include drugs such as phenothiazines (e.g. chlorpromazine), butyrophenones (e.g. haloperidol), thioxanthenes (e.g. flupentixol) and substituted benzamides (sulpiride).[1] SGAs include amisulpride, aripiprazole, clozapine, olanzapine, ▼paliperidone, ▼quetiapine and ▼risperidone.[1] Antipsychotic drug-induced unwanted effects vary depending on the group of drugs used, with some effects being drug-specific. In monitoring people with schizophrenia for unwanted effects of antipsychotics, it is important to bear in mind that the disease itself puts them at a greater risk of developing cardiovascular disease and/or diabetes mellitus, and that they are more likely to die prematurely as a result of these conditions than are people without mental health disorders.[2,3]

Unwanted neurological effects

Extrapyramidal side effects (EPSEs)

Acute antipsychotic drug-induced EPSEs (e.g. parkinsonism, acute dystonia, akathisia) are neurological effects that occur within the first days or weeks of starting therapy; chronic antipsychotic drug-induced EPSEs (e.g. tardive dyskinesia) are those that may occur months or years after starting therapy.[4] At standard doses, SGAs are less likely than FGAs to cause certain EPSEs. For example, depending on the drug used, tardive dyskinesia is up to 15 times more likely with FGAs than with SGAs; however, risperidone, particularly at relatively high doses, appears to carry a greater risk of tardive dyskinesia than other SGAs.[5]

An expert consensus guideline from the USA recommends assessing patients for EPSEs before starting a new antipsychotic, then weekly for at least 2 weeks after initiating therapy (or after a dose change) until the dose has been stabilised.[6] It advises that repeat checks for symptoms suggestive of tardive dyskinesia should be done 6-monthly for FGAs, and 12-monthly for SGAs.[6] Some psychiatry specialists suggest that because inpatients are seen daily by a healthcare professional and that high doses are often used or doses are escalated rapidly in acute psychosis, these people should be monitored for EPSEs every day during initiation of treatment. Validated rating scales are available to assess severity of EPSEs secondary to antipsychotics,[7-9] and should be used where EPSEs are experienced.

Neuroleptic malignant syndrome (NMS)

NMS is a rare, idiosyncratic and life-threatening complication of antipsychotic therapy, characterised by rigidity, hyperthermia and autonomic instability, and usually associated with a raised serum creatine kinase concentration.[10] NMS has been reported to begin as early as 24 hours after initiating therapy and occurs, in almost all cases, within 1 month. It is more likely to develop with high-potency FGAs than with low-potency FGAs[†] or with SGAs, and with parenteral administration, higher titration rates and the cumulative dose of drug administered.[10] NMS occurs less frequently nowadays, probably owing to more conservative prescribing of antipsychotics, increased awareness of the disorder and the move to using SGAs rather than FGAs.[10] If NMS is suspected, immediate management should include stopping the drug and offering supportive medical therapy,[10] and transferring the patient to a medical or emergency unit immediately.

Unwanted cardiovascular effects

QTc prolongation

FGAs are associated with an increased risk of 'sudden cardiac death', thought to be caused by prolongation of the QTc interval and the related risk of ventricular arrhythmias (e.g. torsades de pointes).[11] A large retrospective cohort study comparing patients taking antipsychotics with matched non-users

[†]Low-potency FGAs are typically thought to include chlorpromazine, and high-potency FGAs include haloperidol and pimozide.[1]

showed that the likelihood of sudden cardiac death was dose-dependent, and similar with SGAs and FGAs (around 0.29% vs. 0.14% in non-users).[11] In a separate study, around 28% of inpatients with "psychotic spectrum disorders" had hypokalaemia, a known cause of potentially fatal cardiovascular complications including sudden cardiac death (particularly in patients also taking a drug that can cause arrhythmias).[12]

A National Institute for Health and Clinical Excellence (NICE) guideline on schizophrenia recommends that people who are being started on an antipsychotic should be offered a baseline ECG if this investigation is specified in the summary of product characteristics (SPC) for the drug concerned (e.g. haloperidol[13]); if cardiovascular risk factors are identified during physical examination; if there is personal history of cardiovascular disease; or if the person is an inpatient.[3] Recommendations in the SPC on how frequently to perform ECG recordings are vague; for example, one advises that the investigation should be done "periodically"[14] and another advises it should be done on "an individual basis" (e.g. at dose escalation).[13] For UK practice, the widely used Maudsley Prescribing Guidelines recommend that if QTc prolongation is observed patients should be referred to a cardiologist,[15] and some SPCs provide specific recommendations, such as reducing the dose or stopping the offending drug.[13,14] The Maudsley guidelines also suggest baseline and yearly monitoring of electrolytes.[15] However, the SPCs for SGAs currently marketed in the UK do not make this recommendation.

Hypotension

Chlorpromazine and other older FGAs are more likely to cause hypotension (and more severe hypotension) than are the newer and more dopamine-selective antipsychotics.[16] Of the SGAs, clozapine has the highest tendency to cause hypotension, followed by risperidone and quetiapine;[4] such effects are especially likely to occur in patients with conditions predisposing to hypotension.[17] Compensatory tachycardia often accompanies the fall in blood pressure but tachycardia can also be due to the antimuscarinic (anticholinergic) actions of antipsychotic drugs.[4] To help avoid hypotension, any increases in drug dose should be gradual, and the SPCs advise that patients should have "regular" monitoring of their heart rate and blood pressure.[17-19] If hypotension occurs, the dose should be reduced, if possible.[17-19]

Venous thromboembolism (VTE)

People taking antipsychotics have an increased risk of VTE compared with that in the general population.[20] The absolute increase is low (4 additional cases per 10,000 people treated for 1 year), and higher with SGAs than FGAs (absolute increase of 9 vs. 3 cases per 10,000 treated for 1 year). The risk is highest during the first 3 months of therapy, and is greater in older than in younger patients. VTE is an important, and preventable, cause of morbidity and mortality,[20] and all potential risk factors for it should be identified before, and monitored during, antipsychotic treatment.[21]

Stroke and dementia

In older patients with dementia, antipsychotic use is associated with an increased risk of stroke (e.g. risperidone or olanzapine increase the risk by around three times compared with placebo) and of death (absolute risk increased by around 1–2% compared with no treatment).[22] Evidence from observational studies suggests that other patient groups treated with antipsychotics may also be at an increased risk of cerebrovascular accidents (e.g. older patients without dementia, those taking anticoagulants, people with atrial fibrillation, hypertension or a history of stroke).[23] The risk of antipsychotic-related cerebrovascular accident is highest within the first weeks of starting such treatment.[23] In addition, a recently published double-blind randomised controlled trial showed that outpatients with Alzheimer's disease and psychotic or aggressive behaviour who were treated with the SGAs olanzapine, quetiapine or risperidone experienced greater decline in cognitive function than did those receiving placebo.[24] If antipsychotic drugs are being considered for patients with dementia, then the patient (where possible) and their carer should be informed of the potential harms and the benefits of drug therapy and involved in any decision about using such treatment.[25]

Metabolic problems

A recent *Drug Safety Update* from the UK Medicines and Healthcare products Regulatory Agency warned that some SGAs (i.e. clozapine, olanzapine and quetiapine) are associated with significant weight gain, dyslipidaemia and hyperglycaemia.[2] It stated that available data do not suggest that FGAs have a significant effect on metabolism. However, a systematic review indicated that drugs which cause an increase in body weight were also associated with insulin resistance.[26] It has been suggested that the effects of antipsychotic drugs on lipid metabolism can occur independently of obesity.[27]

A USA consensus guideline recommends that all patients treated with antipsychotics should be screened for impaired glucose tolerance or diabetes before starting treatment and then annually (by measuring fasting blood glucose or glycated haemoglobin [HbA_{1c}] concentration); more frequent monitoring is suggested for those with significant risk factors for diabetes, or those who are gaining weight.[6] In practice, however, fasting blood glucose samples are often difficult to obtain from disorganised or acutely ill patients, and so random samples should be obtained as a minimum, together with HbA_{1c} measurements.[15]

The consensus guideline also recommends monitoring body mass index (BMI) and lipid profiles of all patients with schizophrenia. Patients should be encouraged to monitor and chart their own weight.[6] BMI should be measured when a new antipsychotic is initiated and at every clinic visit for 6 months, and then quarterly once the dose is stable.[6] Lipid screening, including measurement of serum concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides, should be done every 2 years if low-density lipoprotein cholesterol concentrations are within the normal range, or 6-monthly if they are above the normal range.[6] Patients should also be monitored for the impact of metabolic changes on blood pressure by screening for hypertension before initiating antipsychotic treatment and during titration of drug therapy.[15]

Hyperprolactinaemia

All antipsychotics can cause hyperprolactinaemia,[28] the symptoms of which can include amenorrhoea, galactorrhoea, gynaecomastia and sexual dysfunction. Of note, chronic hyperprolactinaemia is associated with the development of osteoporosis and subsequent increased risk of hip fractures.[28] The rates of hyperprolactinaemia associated with FGAs are high, with the condition being reported to occur in up to 72% of patients using haloperidol.[28] Of SGAs, amisulpride and risperidone have the highest propensity to cause hyperprolactinaemia (with up to 100% of patients developing the problem in some studies).[28] However, not all people with elevated prolactin concentrations are symptomatic or concerned by their symptoms, and many remain undiagnosed.[29]

All patients taking antipsychotics need to be asked specifically about symptoms suggestive of hyperprolactinaemia at least yearly,[29] with physical examination and measurement of serum prolactin concentration if such features are present.[6,29] Patients taking antipsychotics associated with a high risk of causing hyperprolactinaemia (e.g. an FGA, amisulpride,[30] or risperidone[19]), should be asked about symptoms more frequently (at every clinic visit during the first 3 months of treatment or until the dose is stable).[6] For such patients, expert consensus from the British Association of Psychopharmacology recommends measuring baseline serum prolactin concentration, with further measurements at 3 months after the dose has become stable and also 3 months after any change in antipsychotic dose.[31] However, the SPCs for amisulpride[30] and risperidone[19] make no recommendation about performing such investigation either before or during treatment.

Pneumonia

Recently published data have suggested that antipsychotic drugs may increase the likelihood of pneumonia.[32] A case-control study in Holland, based on a cohort of 2,560 patients aged at least 65 years who had used antipsychotic therapy, suggested an association between current use of such treatment (either FGAs or SGAs) and the development of pneumonia.[32] The association was greater the higher the antipsychotic dose, and greatest during the first week of treatment. Also, there was an association between development of fatal pneumonia, or pneumonia requiring hospitilisation, and current use of SGAs but not of FGAs.

Specific drugs

Some unwanted effects are specific to individual antipsychotic drugs. For example, treatment with olanzapine is commonly associated with transient, asymptomatic rises in levels of hepatic aminotransaminases.[33] Quetiapine has been associated with severe neutropenia, but this is uncommon and unrelated to the dose of the drug used; most reported cases have occurred within a couple of months of initiation of therapy.[17]

Clozapine

Life-threatening agranulocytosis specific to clozapine occurs in up to 1% of patients treated and so there is an absolute requirement that all patients taking the drug are enrolled in a clozapine-specific monitoring service.[18] Such a service ensures that the patient's white cell count is measured before starting treatment, at least weekly for 18 weeks, at least fortnightly until 52 weeks, and at least monthly thereafter.

Two conditions should be suspected in patients taking clozapine who have persistent tachycardia at rest or palpitations, arrhythmias, chest pain, and other symptoms and signs of heart failure or those that mimic myocardial infarction: myocarditis, which occurs in up to 0.1% of patients, usually developing within 2 months of initiation of therapy; and cardiomyopathy, which occurs in fewer than 0.01% of patients, usually later in treatment. In such cases, clozapine should be discontinued and the patient referred to a cardiologist immediately.

Hypersalivation is common with clozapine (occurring in more than 10% of patients). Impairment of intestinal peristalsis (which occurs in fewer than 0.01% of patients) can range in its effects from constipation to intestinal obstruction, faecal impaction and paralytic ileus.

Practical implications

Before starting antipsychotics, healthcare professionals should counsel patients and carers about common and, rarer but more serious, unwanted effects, and consider offering relevant written information leaflets about the drugs.[34] Patients should be encouraged to report any unwanted effects. A small study found that direct questioning or a more systematic approach to asking about unwanted effects was more effective at getting patients to report such effects than was open questioning.[35]

The British Association for Psychopharmacology recommends monitoring unwanted effects systematically at baseline, at 3 months and annually.[34] However, it states that current guidelines differ as to advice on the nature and frequency of monitoring, and that clinicians need to "balance what is ideal against what is appropriate in a service and for a specific patient".[34] Monitoring for specific unwanted effects should take into account the drug used and the patient's individual risk factors, including the potential for any drug interactions. NICE recommends monitoring the physical health of patients with schizophrenia at least once a year,[3] and investigations for unwanted effects should be, as much as possible, scheduled at the same visit to reduce the need for the patient to return frequently for assessment.

NICE also states that physical health should be monitored by healthcare professionals in primary care, and that those in secondary care have a role in helping to ensure that this is done.[3] Healthcare providers need to be clear about their respective roles and responsibilities in monitoring of a patient's general physical health,[34] and in parts of the UK, shared-care agreements are in place to facilitate such understanding. A large recently published systematic review showed that there is inadequate screening for metabolic problems in people with mental illness treated with antipsychotics.[36] Development of case registers and specific remuneration of GPs for monitoring physical health problems of people with mental health disorders have been introduced to address this issue.[3,37] However, it is unclear whether such interventions have improved outcomes for people with mental health disorders.

Conclusion

Antipsychotic drugs for the management of patients with schizophrenia and other mental health disorders are associated with a wide range of unwanted effects. Compared with first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs) are associated with fewer extrapyramidal unwanted effects, a similar increase in the rate of sudden cardiac death and a higher rate of venous thromboembolism. SGAs are also associated with a higher likelihood of fatal pneumonia in older patients that is not seen with FGAs. Clozapine, olanzapine and ▼quetiapine are associated with weight gain, dyslipidaemia and hyperglycaemia; amisulpride and ▼risperidone have the highest propensity to cause hyperprolactinaemia; and clozapine can cause fatal agranulocytosis. People with Alzheimer's disease are at an increased risk of stroke and of death associated with antipsychotic use, and recent data have shown that treatment with olanzapine, quetiapine or risperidone can increase the rate of cognitive decline in these patients.

Prior to starting antipsychotic therapy, patients should be counselled on the potential unwanted effects and asked to report any that appear to be medication-related. Specific questioning, for example, about symptoms suggestive of hyperprolactinaemia, is more likely to encourage the patient to report such problems than open questioning. Baseline screening for impaired glucose tolerance or diabetes mellitus should be done for all patients treated with antipsychotics and baseline ECG measurement is needed for those on drugs that can cause prolongation of QTc interval (e.g. haloperidol). Thereafter, monitoring will depend on a patient's individual risk factors and the drug used, and on whether the person develops symptoms or signs. All patients taking clozapine must be enrolled in the monitoring scheme for ensuring that white cell counts are measured at regular intervals. A plan for monitoring unwanted effects of antipsychotics needs to be drawn up for each patient, with clarity on the respectively roles of primary and secondary care health professionals.

[R=randomised controlled trial; M=meta-analysis]

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