Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Review of the use of haloperidol in elderly patients with acute delirium

MHRA Public Assessment Report
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Contents

1. Plain language summary

Key messages

The Medicines and Healthcare products Regulatory Agency (MHRA) and the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines (CHM) have reviewed the available evidence and UK safety information for haloperidol when used for the acute treatment of delirium in elderly patients.

Our review did not identify any changes to how haloperidol is allowed to be used for delirium or to the safety information provided for healthcare professionals and patients (the product information). This is because there are already strong warnings and precautions about the potential risks in these documents and these are in line with clinical guidance.

We remind healthcare professionals that special caution is needed when using haloperidol for the acute treatment of delirium in elderly people. This is due to the increased risk of adverse effects in this patient group.

Haloperidol should only be considered for delirium when non-drug methods are not effective, and there are no other conditions present preventing its use (contraindications). Before treatment, it is recommended that patients receive a baseline test of the heart rhythm and electronic activity (electrocardiogram) and that any disturbance to electrolytes (blood salts and minerals) are checked and corrected. The lowest possible dose should be prescribed for the shortest possible time and patients should be frequently reviewed and closely monitored for adverse effects, especially those affecting movement of the body (extrapyramidal effects).

About this medicine

Haloperidol is an antipsychotic medicine. Antipsychotics are used for serious illnesses affecting the way a person thinks, feels, or behaves. Haloperidol works by blocking the action of a chemical called dopamine in the brain. It was first licensed for use as a treatment for schizophrenia in the 1950s.

Haloperidol is available as a tablet, oral solution (taken by mouth), solution for injection into the body, and as a longer-acting solution for injection that is slowly released into the body (depot injection known as haloperidol decanoate).

Haloperidol is mainly used for the treatment of schizophrenia. It is also used, depending on how it is taken, for the treatment of mania in bipolar disorder, treatment of the behavioural symptoms of moderate to severe Alzheimer's dementia, and vascular dementia when non-drug methods have failed and when there is a risk of harm to self or others.

Haloperidol is also used for the acute treatment of delirium when non-drug treatments have failed. Delirium is a sudden state of mental confusion. It may also be called an 'acute confusional state'. There are many potential causes of delirium.

In this Public Assessment Report, we particularly focus on the use of haloperidol for the treatment of acute delirium in frail, elderly people.

Reason for the review and how it was done

The MHRA received a letter from a family following the death of an older relative and concerns around the use of haloperidol in elderly people.

We conducted a comprehensive review of the available evidence regarding the risks of using haloperidol for the acute treatment of delirium in elderly people. We reviewed the current product information and the side effects reported to us by patients and healthcare professionals, in addition to information published by researchers and other medicines regulators. We also considered current clinical and prescribing guidelines to determine whether any changes were required to the UK product information.

We sought advice and endorsement on the assessment from the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines. Clinical experts in psychiatry and elderly care were invited to participate in these discussions. The findings and conclusions of the review are summarised in this report.

We discussed the resulting advice for healthcare professionals with experts in psychiatry and elderly care and with external professional organisations representing clinicians working in neurology, psychiatry, and emergency medicine and the care of elderly people.

Conclusions of the review

Delirium is a complex condition and is more common in patients aged older than 65 years. Haloperidol is only recommended to be used in serious cases of acute delirium and if non-drug treatments have not worked. Research to support the use of medicines for the treatment of delirium is limited and much of the recommendations for use come from clinical guidelines.

Elderly people may metabolise haloperidol differently to other adults and so specific reductions in dosages are recommended in the product information. There are certain conditions, such as Parkinson's disease or Lewy body dementia, or other drugs that make using haloperidol unsuitable.

Haloperidol is associated with some increased risks in elderly people such as side effects affecting the brain and nervous system and the rhythm of the heart. There is further information about these in the product information. Patients receiving haloperidol should be treated with the lowest possible dose for the shortest possible time and carefully monitored for side effects.

This review did not identify any changes necessary to the existing strong warnings and precautions in the product information. However, the review identified that the use of haloperidol in day to day clinical practice in patients with delirium is variable. We have issued a Drug Safety Update article to remind UK healthcare professionals of the safety concerns and to support safe use of haloperidol for the treatment of acute delirium in elderly people.

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The Commission on Human Medicines (CHM) advises government ministers and the MHRA on the safety, efficacy and quality of medicines.

The aim of our Safety Public Assessment Reports is to present evidence-based assessments of safety issues for a particular drug or drug class.

This report provides a summary of the review of available safety data for the use of haloperidol in the treatment of acute delirium in elderly patients. A glossary is provided for an explanation of the terms used in this report.

We understand that there continues to be debate about the most appropriate term to use when discussing the medical care of older people. This report uses the term ‘elderly’ to be consistent with the advice in the product information and current clinical guidance for this medicine. In our assessment of spontaneous reports, we have reviewed data concerning patients aged 60 years and older. In our assessment of the published literature, we used the search terms “elderly or old or aged”.

The information and analyses contained in this report reflects evidence that was available at the time of the review in 2021. The MHRA will continue to monitor the safety of all medicines. The information in this report will not be actively updated with new data or studies unless major new safety information is available that results in critical changes.

3. Background

Haloperidol (also known by the brand-name Haldol) is a first-generation antipsychotic authorised for the treatment of neurological and psychiatric disorders, including the acute treatment of delirium in adults when non-pharmacological treatments have failed. It is part of the butyrophenone group of medicines.

Haloperidol is a prescription-only medicine that is available as tablets, oral solution, solution for injection and as a longer-acting depot solution for injection (haloperidol decanoate). Haloperidol is a potent central dopamine type 2 receptor antagonist and works by blocking dopamine receptors.

The safety profile of haloperidol is well-characterised, and the product information includes strong warnings regarding the increased risk of mortality in elderly patients with dementia, as well as cerebrovascular risks and cardiovascular risks. Recommendations for baseline and monitoring electrocardiograms (ECGs) are also included.

Extrapyramidal symptoms are a particular safety issue associated with the use of haloperidol, as is the risk of orthostatic hypotension, which may increase the incidence of falls in elderly patients. However, it is noted that some of the safety concerns such as increased mortality in elderly people with dementia and cerebrovascular adverse events are also relevant to newer antipsychotics. The MHRA have previously communicated with healthcare professionals on the issue of prescribing antipsychotics to older people with dementia in 2012.

This review was triggered following concerns received from a patient representative regarding the safety of the use of haloperidol for the acute treatment of delirium in older people in the UK. The MHRA assessment was considered by the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines and additional invited experts. Relevant professional organisations were also consulted on the review findings and on the advice issued to healthcare professionals.

4. Delirium

Characteristics and prevalence of delirium

Delirium or ‘acute confusional state’ as it is sometimes known, is a complex disorder defined as an acute disturbance in attention and cognition that develops over a short period of time. The main features of delirium are acute cognitive deficits and altered level of arousal.

The SIGN Guidance on risk reduction and management of delirium notes that up to 50% of patients also experience hallucinations or delusions. Delirium is commonly found in older hospitalised patients and results in significant morbidity and mortality (Witlox J and colleagues, 2010). The prevalence of delirium in the community is estimated to be 1 to 2%, rising to 14% in people over the age of 85 years. In nursing homes, or post-acute care settings, the prevalence may be up to 60% (British Geriatrics Society).

Causes of delirium

The causes of delirium are usually multifactorial and predisposing factors can include older age (over 65 years), dementia or cognitive impairment, vision impairment, alcohol misuse, depression, infection, and surgery, among others (Hshieh TT and colleagues, 2020 and NICE Clinical Knowledge Summary on Delirium).

In people with predisposing factors, a single additional factor may be enough to precipitate delirium. Precipitating factors include infection such as urinary tract infection, infected pressure sores or pneumonia, metabolic disturbance, cardiovascular, respiratory, neurological, endocrine, urological or gastrointestinal disorders. As noted in the NICE Clinical Knowledge Summary on Delirium, severe uncontrolled pain, alcohol intoxication or withdrawal, medication and psychosocial factors may also precipitate delirium.

There are 3 main types of delirium: hypoactive, hyperactive, or mixed behaviour. The hypoactive form is most common in elderly patients (SIGN Guidance, 2019).

Diagnosis of delirium

Delirium may be difficult to diagnose in older people and can occur independently or within the context of dementia which may have similar symptoms, making it challenging to distinguish between the two conditions (Young J and Inouye SK, 2007). The most recent National Audit of Dementia Care in General Hospitals identified that 58% of notes of people with dementia admitted to hospital showed that an initial assessment for delirium had taken place on or during admission.

Dementia is a leading risk factor for delirium (Fong TG and colleagues, 2017). There are, however, key differences – delirium has an acute and rapid onset and patients exhibit inattention, whereas the onset of dementia is more gradual. Evidence suggests that delirium can lead to permanent cognitive impairment and dementia (Inouye SK and colleagues, 2014). Patients with dementia who experience delirium may have worsened cognitive and functional decline, and increased length of hospital stay, hospital readmission rate, institutionalisation rate, and mortality (Hshieh TT and colleagues, 2020).

Various tools are used to detect and assess delirium. These include the 4As test (Arousal, Attention, Abbreviated Mental Test 4, Acute change) and the Confusion Assessment Method (CAM) (SIGN Guidance, 2019).

Prevention and treatment of delirium

Multicomponent non-pharmacologic interventions have been found to be effective for delirium prevention (Hshieh TT and colleagues, 2020). If symptoms impose a safety risk for the patient or medical staff, then antipsychotic treatment may be useful but only in a time-limited manner and at the lowest possible dose (Kukolja J & Kuhn J, 2021).

In intensive care units, antipsychotics are a treatment option for delirium. Newer antipsychotics may be preferred over first-generation antipsychotics (such as haloperidol) because of the lower incidence of extrapyramidal adverse effects including akathisia or restlessness (Santos C and Mariah R, 2021). Haloperidol is the most widely used drug in the treatment of delirium (Rivière J and colleagues, 2019).

Clinical guidelines

There are several clinical guidelines that specifically address delirium. The NICE Guideline Delirium: prevention, diagnosis and management [CG103] (published 28 July 2010; updated 14 March 2019) covers diagnosing and treating delirium in people aged 18 years and over in hospital and in long-term residential care or a nursing home. It advises that after all assessments for underlying cause and if non-pharmacological treatment/de-escalation options are found to be ineffective or inappropriate then short-term haloperidol (usually for 1 week or less) is recommended. This should be started at the lowest clinically appropriate dose and titrated cautiously according to symptoms.

Guidance on the risk reduction and management of delirium is also available from SIGN [guideline 157] (published March 2019). This includes the Scottish Delirium Association delirium management pathway, which, following assessment and investigation, recommends that:

- non-pharmacological practices be tried before pharmacological interventions are considered
- all patients at risk of delirium should have a medication review conducted by an experienced healthcare professional
- if a patient's symptoms threaten their safety or the safety of others, a low dose of medication should be used and reviewed every 24 hours
- for unmanageable agitation/distress, haloperidol is recommended as first line with a note that it is contraindicated in combination with QTc prolonging drugs

This guideline notes that the evidence for pharmacological treatment in urgent situations is insufficient to support a recommendation but expert opinion supports a role for medication in specific situations such as in patients in intractable distress and where the safety of the patient and others is compromised.

Other guidelines including The Maudsley Prescribing Guidelines in Psychiatry, the WHO guideline on essential medicines and palliative care and the Scottish Palliative Care Guidelines on delirium recommend haloperidol as a first line agent.

COVID-19 and delirium

During the coronavirus (COVID-19) pandemic, haloperidol has also been used for the treatment of delirium associated with COVID-19. We are aware that the British Geriatrics Society, European Delirium Association, and Old Age Psychiatry Faculty (Royal College of Psychiatrists) has produced consensus guidance on managing delirium in confirmed or suspected cases of COVID-19 (published 19 March 2020). Further consideration of information around use in COVID-19 was outside the scope of this review.

5. Methods

Yellow Card data

The Yellow Card scheme run by the MHRA is the UK system for collecting and monitoring information on safety concerns such as suspected side effects involving medicines. All Yellow Card reports received are entered onto the MHRA's adverse drug reaction database so that they are available for signal detection.

It is important to note that a reported reaction or case does not necessarily mean it has been caused by the drug or vaccine, only that the reporter had a suspicion it may have. Underlying or concurrent illnesses may be responsible and such events can also be coincidental. Additionally, it is also important to note that the number of reports received via the Yellow Card scheme does not directly equate to the number of people who suffer adverse reactions, and therefore cannot be used to determine the incidence of a reaction. Adverse drug reaction reporting rates are influenced by the seriousness of these reports, their ease of recognition, the extent of use of a particular drug or vaccine and may be stimulated by promotion and publicity about a drug or vaccine.

The MHRA Yellow Card Database was reviewed for all UK reports including haloperidol as the suspect drug from the first report in 1964 up to 30 June 2021. This search was then narrowed to consider only those reports relating to patients aged 60 years and older.

Additional searches were also conducted for the same reporting period to identify reactions using the higher-level term of "medication errors and other product use errors and issues" and also reactions reported in the "overdoses and underdoses" category.

Usage

Data on haloperidol prescriptions issued between 1 July 2016 and 30 June 2021 were extracted from the CPRD AURUM database using the June 2021 database version. Drug usage in terms of patient exposed was also derived from the ePACT2 database, which is held by the NHS Business Services Authority (NHSBSA). Drug usage in the UK was derived from the IQVIA MIDAS database, which captures the volume drug dispensed by prescription in UK and hospital pharmacies.

Literature searches

A ProQuest Dialog search was conducted on 19 July 2021 using the following databases: Allied & Complementary Medicine, COVID-19 Research, DH-DATA: Health Administration, Medical Toxicology & Environmental Health, Embase and Medline. The search terms haloperidol, elderly or old or aged, and dementia or delirium were used to search for English-language articles.

The Cochrane Library was also reviewed, and relevant clinical guidelines were identified from the NICE and SIGN websites.

6. Review of Yellow Card data

Yellow Card data

Up until 30 June 2021, a total of 1334 UK Yellow Card reports had been submitted in association with the use of haloperidol as suspect drug, describing 3352 suspected adverse drug reactions (ADRs). The highest number of reports were reported in the 'Nervous system disorder SOC (system organ classes)' with 1004 reports. In 108 reports, the suspected ADRs had a fatal outcome (25 of which were in the Nervous system disorder SOC).

Of the 1002 reports where the age was known, 240 occurred in patients aged 60 years of age and older. Data for all spontaneous suspected adverse drug reactions for haloperidol reported via the Yellow Card scheme are available on the MHRA's Interactive Drug Analysis Profiles.

When narrowing the SOC review to patients aged 60 years or older only, the largest number of reports remains in the nervous system disorders class. Of these, reactions were most frequently categorised as movement disorders (including parkinsonism) (n=76) and the highest number of reports were of extrapyramidal disorder (n=21). The classes of general disorders and administration site conditions and psychiatric disorders detailed the second and third largest number of reactions respectively.

The review noted that the reported side effects are consistent with the known safety profile of haloperidol and no new, unlisted safety issues or concerns were identified.

A total of 44 reactions were identified in the "Medication errors and other product use errors and issues" high-level term (HLT) category and none of these had a fatal outcome.

There are 18 reported reactions in the "Overdoses and underdoses" HLT. Of these, 4 had a fatal outcome – 3 due to "overdose" and 1 "intentional overdose". There were 6 cases of interest relating to elderly patients, of which 2 were fatal. One of these led to the initiation of this review. This was a case of a female patient in her early 90s who was admitted to hospital with a urinary tract infection and delirium. She was prescribed antibiotics to treat the infection and haloperidol to treat the delirium. The patient was prescribed a larger dose of haloperidol than recommended in the product information. The drug error was noted, and the drug was stopped. The patient had several comorbidities and went on to develop aspiration pneumonia and died 5 days later in hospital. The Coroner concluded that the patient died from aspiration pneumonia contributed to by a number of factors and that haloperidol may also have had a minimal impact on her developing pneumonia.

The other fatal case which was identified was of a patient aged older than 60 years who died from an overdose that was not related to haloperidol.

Our review of the other cases did not identify any other reports of such a large overdose. However, medication errors were reported in cases where haloperidol was contraindicated but had been prescribed in patients with Parkinson's disease and Lewy body dementia.

The assessment of the evidence from Yellow Card reports did not identify any new information regarding the use of haloperidol in elderly patients in the treatment of delirium. The review noted that under-reporting may be significant in this patient population due to the nature of the condition.

Usage

It was not possible to obtain accurate exposure data specifically relating to the use of haloperidol for delirium in elderly people. Haloperidol exposure occurs within the emergency care and hospital settings but also within the care home setting. The available data suggest that haloperidol is prescribed more frequently for patients with the dementia term used in their diagnosis, than for delirium. However, as these conditions often co-exist, patients with dementia may also be experiencing delirium.

7. Review of published literature

Efficacy

In 2018 NICE conducted a comprehensive review of studies relating to the efficacy of haloperidol for the treatment of delirium prior to the update of the NICE guideline in March 2019. Therefore, we did not further consider literature on efficacy published before the data lock point of 1 May 2018. It is noted that the NICE guidance concludes that there is limited evidence regarding the use of pharmacological interventions in clinical practice to manage the symptoms of delirium and that further research is required in this area.

Systematic reviews

A systematic review on the use of haloperidol to treat critically ill patients with delirium was recently published (Barbateskovic M and colleagues, 2020). This found the evidence in this area to be sparse, of low quality, and inconclusive. No particular reference was made in relation to the evidence base in this area for elderly patients.

A recent Cochrane Review (Finucane A and colleagues, 2020) evaluated the effectiveness and safety of drug therapies, including haloperidol, to manage delirium symptoms in terminally ill adults and also concluded that no high-quality evidence was available.

In their 2018 Cochrane Review, Burry and their colleagues considered the use of antipsychotics for the treatment of delirium in hospitalised patients not in the intensive care unit (ICU) and excluded critically ill populations. The Cochrane review identified 9 studies with 727 participants assessing antipsychotics for delirium treatment: 4 of the trials compared an antipsychotic to another drug class or placebo and 7 of the 9 compared a first-generation antipsychotic to a second-generation antipsychotic. No evidence was identified to support or refute the suggestion that antipsychotics shorten the course of delirium in hospitalised patients. The reviewed studies suggest that antipsychotics do not reduce the severity of delirium or resolve symptoms compared to non-antipsychotic drugs or placebo or lower the risk of dying. No evidence was identified to support or refute the suggestion that antipsychotics shorten hospital length of stay or improve health-related quality of life. No statistically significant differences in effect size were noted when comparing first-generation and second-generation antipsychotics. The authors note that the overall quality of the available evidence was poor, and many clinically relevant outcomes were not reported. Not enough studies were identified to enable any sub-group analyses of outcomes in elderly patients.

Nikooie and colleagues' systematic review aimed to evaluate the benefits and harms of haloperidol and second-generation antipsychotics compared with placebo and other antipsychotics for treating delirium in hospitalised adults. A total of 16 randomised controlled trials and 10 observational studies of hospitalised adults were identified as meeting the eligibility criteria.

The systematic review found no differences for haloperidol and second-generation antipsychotics, compared with placebo, in sedation status, delirium duration, hospital length of stay, or mortality. There was no difference in delirium severity and cognitive functioning for haloperidol versus second-generation antipsychotics or no evidence for antipsychotics versus placebo. They also found little evidence of demonstrated neurological harms associated with short-term use of antipsychotics for treatment delirium in adult inpatients.

The authors concluded that for some clinically important outcomes and specific patient subgroups (such as older adults and palliative care patients), there was insufficient or no evidence, emphasising the need for continued future research in the field. This review was consistent with the Cochrane review, which found limited evidence relating to elderly patients. The authors also noted that the studies reviewed were heterogenous and they could not evaluate benefits and harms in the context of different types of delirium and agitation status. This paper was part of a larger comparative effectiveness review by Neufeld and colleagues, 2019. The conclusion that further studies with larger sample sizes are needed was also noted in other systematic reviews of the literature such as that by Shen and colleagues, 2018.

Other literature

Lodewijckx and colleagues recently reviewed the literature regarding pharmacological treatment for hypoactive delirium in adult patients. Only 4 articles were considered to meet the selection criteria – 2 cohort studies and 2 randomised controlled trials. The authors noted that haloperidol was not found to show any significant difference compared with placebo. This review further supports the conclusion that there is a lack of relevant study data and further research is needed.

Safety

The evidence base relating to the safety of haloperidol in elderly people is more robust than that for efficacy. Reports have indicated for some time that there is an increased risk of serious adverse events associated with antipsychotics, especially in frail elderly people (Wang P and colleagues, 2005; Gill SS and colleagues, 2007; Ray WA and colleagues, 2009; and Mittal V and colleagues, 2011).

A retrospective observational study published earlier this year (Jenraumjot R and colleagues, 2021) aimed to identify the type of “drug-related problems” concerning antipsychotic use among elderly patients (aged older than 60 years) with delirium. A total of 159 patients taking haloperidol were included in the study. Issues relating to duration, dosage, and route of administration of haloperidol were identified.

Extrapyramidal symptoms and QTc interval prolongation were identified as 2 safety concerns that may be severe in the elderly population.

Increased mortality in people with dementia

Studies suggest that treatment of elderly patients with haloperidol is associated with increased mortality (Gill SS and colleagues, 2007 and Schneeweiss S and colleagues, 2007). The MHRA considered this issue in 2008 and the UK product information was updated to include safety warnings regarding this risk.

Cerebrovascular risk

The evidence relating to an increased risk of stroke in elderly patients taking antipsychotics including haloperidol is also well established. Most of the studies in this area were conducted in the elderly population with dementia.

A recently published real-world study by Fife and colleagues from a US health insurance claims database estimated stroke risk associated with new exposure to haloperidol or older antipsychotics, versus newer antipsychotics in patients aged 65 years or older, regardless of dementia status.

The authors found that the propensity score (PS)-matched calibrated hazard ratio (cHR) for stroke in patients exposed to older antipsychotics versus newer antipsychotics was 1.08 (95% confidence interval (CI) 0.75 to 1.55) with Sentinel PS strategy and 1.31 (95% CI 1.07 to 1.60) with the adapted PS strategy . The cHR for stroke in patients exposed to haloperidol versus newer antipsychotics was 1.69 (95% CI 1.08 to 2.75, Sentinel PS strategy) and 1.45 (95% CI 1.17 to 1.80, adapted PS strategy).

The risk of stroke in elderly new users of haloperidol and other older generation antipsychotics was elevated as compared with new users of newer antipsychotics. Most of the patients in the older antipsychotic cohort were haloperidol users, therefore the authors conclude that this cannot be considered strong evidence of a class effect.

The findings of this study are consistent with wording already present in the UK product information, which states that an increased stroke rate was found in elderly patients and this increase may be higher with all butyrophenones, including haloperidol.

Cardiovascular risk

There are extensive data linking the older generation antipsychotics to an increased risk of sudden cardiac death (Ray W and colleagues, 2009). QTc interval prolongation is a known risk associated with antipsychotics, including haloperidol. The review by Nikooie and colleagues, 2019, noted a tendency for more frequent potentially harmful cardiac effects. A Europe-wide review of effects of antipsychotics on the heart was completed in 2005. The UK Summary of Product Characteristics contains extensive wording regarding these risks, including relevant contraindications and safety warnings.

Extrapyramidal effects

Haloperidol is known to be associated with extrapyramidal adverse effects (Devlin JW and colleagues, 2012). It is suggested that newer antipsychotics are preferred over first-generation antipsychotics because of their lower incidence of extrapyramidal adverse effects (Santos C and Mariah R, 2021). The Cochrane Review by Burry and colleagues noted that pooled results from the identified trials showed no statistically increased risk of extrapyramidal symptoms with first-generation antipsychotics compared to second-generation antipsychotics (relative risk (RR) 12.16, 95% CI 0.55 to 269.52). However, this was based on a comparison of 2 studies and the evidence that was identified was assessed as being of very low quality.

Pneumonia and aspiration pneumonia

A systematic review and meta-analysis by Dzahini and colleagues in 2018 investigated the association of antipsychotic exposure with the incidence and mortality of pneumonia. In total 19 studies were included in the systematic review and 14 in the meta-analysis, including 206,899 patients. Of the 14 studies, 10 included patients aged older than 65 years and 2 further studies did not specify age but are likely to have largely assessed patients older than 65 years. Exposure to both first-generation and second-generation antipsychotics was reported to be associated with an increased pneumonia risk compared with no antipsychotic use. Antipsychotic use did not significantly affect the fatality rate from pneumonia compared with no antipsychotic use, however, the authors note that only 2 studies assessing this were included in the meta-analysis and they reported opposite effects. Haloperidol was one of the antipsychotics included in at least 2 of the studies analysed in the systematic review and meta-analysis.

Although the outcome of this meta-analysis suggested that both first-generation and second-generation antipsychotics are associated with an increased risk of pneumonia, the authors conclude that causality remains unproven given the lack of data from randomised controlled trials and a failure of observational studies to control for relevant confounders like tobacco use and weight.

A retrospective cohort study was conducted by Herzig and colleagues in 2017 in a large medical centre to investigate the association between antipsychotic use and aspiration pneumonia in non-psychiatric, adult hospitalisations. An abstract representing an earlier version of the data was included in the Dzahini review. The cohort included 146,552 hospitalisations. Antipsychotics were used in 10,377 (7.1%) of the hospitalisations (80% second generation, 35% first generation). After adjustment, antipsychotic exposure was significantly associated with aspiration pneumonia (adjusted OR (aOR) 1.5, 95% CI 1.2 to 1.9). The authors noted that although the relationship between antipsychotic use and aspiration pneumonia did not differ significantly according to age, individuals aged 75 years had more than triple the incidence of aspiration pneumonia than those younger than 65 years. The authors note that because of this, the absolute risk of aspiration pneumonia attributable to antipsychotic exposure is much greater for older adults than for younger adults.

The meta-analysis suggests that first-generation and second-generation antipsychotics are associated with an increased risk of pneumonia. However, the authors do not suggest a causal relationship due to the lack of data from randomised controlled trials and as the observational studies identified did not control for confounders such as tobacco use and weight. The results of the cohort study support an association between antipsychotic use and aspiration pneumonia in hospital and the authors suggest that antipsychotic exposure is associated with greater risk, particularly in older adults. Further studies may be necessary to confirm whether there are differences in the risk of pneumonia associated with individual antipsychotics and to identify possible risk factors in different patient subgroups.

Guidance from international regulators

Information was also considered from international regulators other than the MHRA and the European Medicines Agency, specifically that from the US Food and Drug Administration (FDA).

In the USA, haloperidol is licensed for use in the treatment of schizophrenia and for the control of tics and vocal utterances of Tourette’s disorder. The FDA-approved package insert (equivalent to product information) has a black box warning (used for serious side effects) regarding increased mortality in elderly patients with dementia-related psychosis. The FDA issued alerts regarding this warning in 2005 and 2008.

The increased mortality risk in elderly patients with dementia is reflected in the UK product information. Review of the FDA safety information did not raise other major safety concerns not already considered.

Additional evidence

Apart from the data mentioned above, further evidence provided by members of the public, older literature references and other supporting documents were also assessed during the review.

8. Discussion

Delirium is a complex condition associated with increased mortality. Delirium is known to be common in elderly patients, particularly those who are frail. Elderly patients are at an increased risk of delirium due to several factors including polypharmacy, comorbidities, frailty, and acute illness (Chyou TY and Nishtala P, 2021). There is unlikely to be one cause or treatment for all delirium, and different types of delirium may respond in different ways.

Haloperidol has been licensed for more than 50 years and has a broad range of indications, including as a second-line treatment for acute delirium when non-pharmacological treatments have failed. Usage data suggests haloperidol is used frequently in elderly patients, but it is difficult to determine accurate data on usage in the treatment of delirium.

Use of pharmacological treatments such as haloperidol in the treatment of elderly patients with delirium may be considered controversial and have been associated with use of the term “chemical cosh”. The current NICE guideline for treatment of delirium clearly emphasises that non-drug treatment plays an important role and should be attempted if possible before considering drug treatment for delirium. This guidance is consistent with the current licensed indication for haloperidol. However, there are clinical scenarios where it is necessary to ensure that a particularly agitated patient is safe to allow a full assessment to be undertaken and to treat the underlying cause of their delirium. It has been used during the COVID-19 pandemic for the treatment of delirium and is cited as a first-line treatment option in clinical guidelines specific to the treatment of COVID-19 delirium.

UK Yellow Card data have been reviewed and show that suspected adverse drug reactions to haloperidol occur most frequently within the nervous system organ class and this is consistent with the known safety profile. However, due to the nature of the conditions for which haloperidol is prescribed, under-reporting is expected, particularly in elderly patients. In patients older than 60 years of age, a total of 561 reactions, including 26 fatal reports have been reported. The largest proportion (170 reports, 8 fatal reports) were reported to the nervous system organ class category. No new adverse reaction reports of concern were identified.

The safety concerns relating to the use of haloperidol in the treatment of elderly patients are well-known and particularly relate to cerebrovascular and cardiovascular risks, extrapyramidal symptoms, and the increased mortality risk in elderly patients with dementia. A review of the literature has not identified any other new safety issues.

There is some evidence for an association between pneumonia and aspiration pneumonia and antipsychotic use. An association between antipsychotics and pneumonia, particularly aspiration pneumonia in older adults hospitalised for non-psychiatric reasons has been reported (Herzig and colleagues, 2017). Although the mechanisms for this are not clear, antipsychotics could increase the risk by multiple mechanisms including impairment of swallowing and cough reflexes, sedation and dysphagia. However, the authors of a recent

meta-analysis (Dzahini and colleagues, 2018) which reported an association between both older and newer antipsychotics and pneumonia, did not claim a causal association due to the nature and quality of the studies included in the analysis. The authors of this study also postulate that the underlying psychiatric illness rather than the pharmacological treatment may increase the risk of pneumonia.

Pneumonia or aspiration pneumonia is a listed adverse reaction for some of the second-generation antipsychotics including risperidone, but the information is not consistent across these newer antipsychotics. The UK product information for haloperidol does not list pneumonia or aspiration pneumonia but it is noted that the US product information equivalent states that a number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs including haloperidol. The Yellow Card data assessed in this review identified a limited number of cases which do not provide any significant evidence to support adding the risk of pneumonia or aspiration pneumonia for haloperidol. However, this issue will be kept under review.

To date, studies on the efficacy of antipsychotics, including haloperidol, have been found to be of heterogenous and inconclusive. It is widely acknowledged in the literature identified, as well as noted in the NICE guideline recommendations and in the Burry and colleagues Cochrane review, that further research is needed to determine which is the most effective medication (first-generation antipsychotics, second-generation antipsychotics, or benzodiazepines) compared with placebo or each other for treating delirium.

A European Article 30 assessment in 2017 also noted that results of placebo-controlled studies are not convincing of an effect in patients with delirium. However, the limitations of these trials were acknowledged by the Committee for Medicinal Products for Human Use (CHMP) in view of the difficulties to conduct adequate clinical trials in this indication and therefore the indication of acute treatment of delirium where non-pharmacological treatments have failed was included based on expert opinion.

Burry and colleagues noted that good quality evidence for the treatment of delirium for hospitalised non-ICU patients with antipsychotic drugs remains limited and fraught with issues. They had intended to undertake a subgroup analyses as part of their review to determine if there were differences in effect or safety in older populations or patients with dementia, but this could not be addressed due to a lack of data.

The authors also note that they had anticipated finding more evidence in these populations where delirium is common. A similar finding was also noted by Nikooie and colleagues, and there is an apparent need for further study in this area. Haloperidol is also widely used in the ICU setting to treat delirium. However, based on the limited evidence identified in this review, there may be a need for further study to fully understand the impact of its use.

A protocol was published in 2020 (Smit and colleagues, 2020) outlining a large, multi-centre, randomised controlled trial to better define the efficacy and safety of haloperidol to treat delirium in critically ill adults in the Netherlands.

Limited evidence suggests the use of newer antipsychotics may be growing but further research in this area is also needed (Rivière and colleagues, 2019) and haloperidol continues to be widely used. Indeed, it is noted that during the development of the most recent NICE guideline, one topic expert suggested that risperidone could be used for delirium. However, at this time it was concluded that the evidence remained insufficient to recommend changing the guideline.

The study of patients with delirium remains challenging. Nevertheless, it is important to note that newer antipsychotics are not currently licensed for use in acute delirium.

NICE also recommended further study be conducted in people in long-term care to determine the prevalence of delirium in this setting and if the presence of delirium is a prognostic factor for death, dementia, admission to hospital, falls and other adverse outcomes. Further research in this area will be of importance in the treatment of elderly patients.

The product information for haloperidol was also reviewed. The Summary of Product Characteristics for haloperidol currently includes clear information regarding the pharmacokinetic profile in elderly patients and the necessary dosage adjustments to minimise risks due to higher plasma levels. Advice recommends use of the lowest possible dose, for the shortest possible time. The indication for delirium is necessarily strict and consistent with clinical guidelines. There are also clear contraindications for the use of haloperidol which may be particularly relevant for elderly patients and STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria are available in the BNF to aid with identifying cases where a prescription may be potentially inappropriate.

Haloperidol is a potent antipsychotic associated with a number of side effects. The safety profile is well-characterised, and the product information includes strong warnings regarding the increased risk of mortality in elderly dementia patients, cerebrovascular risk and cardiovascular risks. Recommendations for baseline and monitoring ECGs are also included.

Extrapyramidal symptoms are a particular issue associated with the use of haloperidol, as is the risk of orthostatic hypotension which may increase the incidence of falls in elderly patients. However, it is noted that some of the safety concerns such as increased mortality in older people with dementia and cerebrovascular adverse events are also relevant to other, newer antipsychotics such as risperidone. The two groups of antipsychotics have different mechanisms of action.

It is clear from the safety profile that haloperidol should only be used in the short-term for delirium when non-pharmacological methods have been unsuccessful and with particular caution in elderly people given that pharmacokinetics may increase the incidence of some of the more serious adverse effects.

With respect to overdose, all antipsychotics are known to cause QTc prolongation (even at therapeutic doses). although haloperidol is in the highest risk group for this compared to most other antipsychotics and has stronger warnings and monitoring requirements accordingly.

In summary, this review, including a thorough analysis of the literature and Yellow Card reported data, has not identified any new safety concerns. There is some evidence from the literature regarding the association between antipsychotic use and pneumonia which, at the least, indicates that there should be an awareness of a potential greater risk of this particularly in elderly people. However, the data does have limitations and it would be appropriate to review the evidence for all antipsychotics, for a consistent approach to description of this event in product information.

Data supporting the use of haloperidol in delirium are very limited due to the poor quality of trials, however, when caring for individuals who pose a risk to themselves and others, there are few alternatives and data regarding other pharmacological treatments are also limited.

9. Conclusions

Evidence regarding the efficacy of haloperidol in the treatment of delirium in elderly patients is limited. Further studies would be helpful in this area. However, it is acknowledged that this is a difficult area of research and expert opinion remains important to guide clinical decisions.

Haloperidol is recommended as a second-line treatment for acute delirium in current clinical and prescribing guidelines (with the exception of COVID-19 treatment guidance). This review has not identified any new safety concerns from the available pharmacovigilance safety data or literature.

The current Summary of Product Characteristics is considered adequate in terms of the currently licensed indication for delirium, the recommended dosage modifications for elderly patients and on the basis of extensive warnings regarding safety of use in elderly patients. Appropriate risk minimisation measures are already in place with respect to cardiac monitoring.

A Drug Safety Update article has been published to highlight to UK healthcare professionals the safety issues associated with the use of haloperidol for the treatment of acute delirium in elderly people. The aim of the article, together with publication of this assessment report, is to raise awareness of these important safety issues and emphasise current clinical best practice as well as the need for further research. Stakeholder engagement has also been undertaken to ensure that these are message are clear for healthcare professionals who use haloperidol for delirium.

We will continue to monitor the safety and use of haloperidol in elderly patients and keep this under review, particularly with respect to any new studies regarding the efficacy of different types of antipsychotics in the treatment of delirium.

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11. Glossary of Terms

Acute treatment
Treatment for a rapidly developing condition that may only be required for a short period of time.

Akathisia
An inability to remain still.

Antipsychotic
A medicine mainly used to treat mental health conditions such as schizophrenia and other psychoses, agitation, severe anxiety, mania and violent or dangerously impulsive behaviour. They also used to treat nausea and vomiting, intractable hiccough and for the management of pain and associated restlessness in palliative care.

British National Formulary (BNF)
A UK pharmaceutical reference containing information and advice on prescribing and pharmacology of medicines.

Cardiovascular risks
Risks that may increase the likelihood of conditions affecting the heart or blood vessels.

Cerebrovascular risks
Risks that may increase the likelihood of conditions affecting the supply of blood to the brain.

Clinical data or clinical studies
Data on the effects of medicines that come from studies of people taking the medicines. This includes data from clinical trials and epidemiological studies.

Clinical trial
A research study that tests the effectiveness and safety of medicines in humans.

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products. CHM is an advisory non-departmental public body, sponsored by the Department of Health and Social Care.

Comorbidity/Comorbidities
Comorbidity means more than one disease or condition is present in the same person at the same time. Conditions described as comorbidities are often chronic or long-term conditions.

Confidence interval
A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between 2 groups, and usually accompany ratio values such as odds ratios, hazard ratios and ‘observed versus expected’ ratios. A 95% CI suggests that there is a 95% chance that the real difference between 2 groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

Confounds/confounding/confounded
Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

Contraindicated/Contraindication
When a drug should not be used in a specific situation, condition or group of people because it may be harmful to the person.

Delirium
A state of mental confusion that starts suddenly and is caused by a physical condition. Also known as ‘acute confusional state’.

Delusion
Where a person has an unshakeable belief in something untrue.

Dementia
A group of related symptoms associated with an ongoing decline of brain functioning.

Dopamine
A natural chemical in the brain that regulates aspects of behaviour including mood and emotions, control of sleeping and wakefulness and control of feeding.

Electrocardiogram (ECG)
A test used to check the rhythm and electrical activity of the heart.

Electrolyte
A substance such as sodium, potassium or chloride which helps to regulate the balance of body fluids.

Extrapyramidal movement disorders
Involuntary movements that can occur as a side effect of antipsychotic medicines. These side effects are associated with the extrapyramidal system of the brain's cerebral cortex.

First-line treatment
The first type of treatment a person receives for a disease or medical condition.

Frailty
A loss of resilience that means people don't bounce back quickly after physical or mental illness, an accident or other stressful event.

Hallucinations
When someone sees, hears, smells, tastes or feels things that do not exist outside of their mind.

Hazard ratio
A measure of risk of an event occurring. Hazard ratios higher than 1 suggest increased risk, equalling 1 suggest equal risk, and lower than 1 suggest decreased risk. Usually accompanied by a 95% confidence interval (CI).

Indication
The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

Meta-analysis
A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

Morbidity
A disease or a symptom of disease, or the level of disease within a population.

Mortality
A death from a certain cause or the number of deaths in a certain group of people in a certain period of time.

National Institute for Health and Care Excellence (NICE)
The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

Orthostatic hypotension
A drop in blood pressure that happens upon standing up from sitting or lying down.

Pharmacological treatment/intervention
The treatment of a health condition using medicines.

Product information
Documents providing officially approved information for healthcare professionals and patients on a medicine. The product information includes the Summary of Product Characteristics, Patient Information Leaflet, and product labelling. The product information for medicines is available at: https://www.gov.uk/guidance/find-product-information-about-medicines.

QTc
A measurement made using an electrocardiogram. This measurement provides information about the electronic impulses controlling the heart rhythm. When the QTc interval is prolonged, the heart rhythm can become disrupted and cause arrhythmia.

Randomised controlled clinical trial
A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention.

Risk factor
A substance or activity that increases the likelihood of someone developing an illness or medical condition.

Risk Ratio/Relative Risk
A risk ratio (RR), also called relative risk, compares the risk of a health event (disease, injury, risk factor, or death) among one group with the risk among another group.

Schizophrenia
A severe long-term mental health condition that causes a range of different psychological symptoms.

Second-line treatment
The second type of treatment a person receives for a disease or medical condition.

SIGN
Scottish Intercollegiate Guidelines Network aims to improve the quality of health care for patients in Scotland by reducing variation in practice and outcome, through the development and dissemination of national clinical guidelines containing recommendations for effective practice based on current evidence.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use.

Systematic review
A review of the published scientific literature that aims to find as much as possible of the research relevant to a particular research question and based on appraisal of the research summarises the main findings (qualitative or quantitative).

Yellow Card scheme
The MHRA's scheme for healthcare professionals and members of the public to report suspected adverse reactions for a medicine or vaccine, as well as medical devices and other products.

Alternative format versions of this report are available on request from info@mhra.gov.uk.