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Haloperidol for delirium prevention: uncertainty remains

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Key Points:

- There is insufficient evidence to support the use of haloperidol for prevention of delirium in older people in hospital
- Delirium is a heterogeneous condition and research is hindered by poorly understood pathoetiology
- Future research should focus on developing and testing hypotheses likely to lead to viable biomarkers and drug targets
- Editorial to accompany Age and Ageing paper: *Haloperidol versus placebo for delirium prevention in acutely hospitalised older at risk patients: A multi-centre double-blind randomised controlled clinical trial.*

Between one in four and one in five older people admitted to hospital will experience the unpleasant condition of delirium (1,2). Delirium has a significant impact on the health service (extended lengths of stay, requirement for increased nursing resource). It is a cause of distress for patients and their carers, and has been associated with poor outcomes (accelerated cognitive decline, new care home and admission and death) (3). Despite this, research into delirium is limited relative to the size of the problem; there are gaps in the evidence base and considerable uncertainty as to how best to prevent and manage delirium across healthcare settings.

Once established, there are no effective treatments for delirium. International guidance advises the use of antipsychotics (haloperidol or olanzapine) at the lowest possible dose, and only as a last resort where de-escalation measures have failed to control distressing or dangerous behavioural symptoms of delirium (4). Emphasis is therefore placed on the importance of delirium prevention.

Research into strategies for delirium prevention has focused on two key areas: multicomponent delirium prevention interventions, and pharmacological agents. Meta-analyses have shown

multicomponent interventions (MCI) to be effective in reducing delirium incidence by about a third, and this is a widely advocated approach (5). However, there are implementation challenges (6) and some doubt over the effectiveness of multicomponent interventions in improving longer term outcomes, perhaps due to the confounding effects of frailty (7). The evidence for pharmacological prophylaxis is even less convincing. Previous trials of antipsychotics for delirium prevention have taken place in surgical settings (8,9) and ICU (10) and generalizability to older people in other hospital settings is limited. Studies have tended to be underpowered, giving mixed and inconclusive results. Consequently, antipsychotics are not currently recommended for routine delirium prevention.

Adding to the existing evidence base, in this issue, Schrijver et al report results of their double-blind, randomised placebo-controlled trial of haloperidol vs usual care for prevention of delirium in at-risk hospitalised older inpatients (aged ≥ 70) in medical and surgical settings (17). This is the first trial of haloperidol for delirium prevention in a general medical setting, and this is a compelling rationale for having undertaken the study. All patients were provided with a 'standard' non-pharmacological (multicomponent) delirium prevention intervention and then randomly assigned to haloperidol 1mg (n=119) or placebo (n=126) twice daily for a maximum of 7 days post-randomization. Intention-to-treat analysis included 118 in the intervention group (112 received the intervention), and 124 in the control group (117 received placebo). Reasons for exclusion post-randomisation were balanced between groups. There were no significant adverse events or side-effects warranting withdrawal from the study. Participants with severe communication difficulties, and those with vascular dementia were excluded from the study – these subgroups are at high risk of delirium and this may have diluted any treatment effect. In addition, overall incident delirium may have been lower than previous estimates as usual care in both groups included 'standard' non-pharmacological prevention strategies.

The primary outcome was delirium incidence detected through daily screening with the Delirium Observation Screening Scale (DOSS) (11) and confirmed by a clinician against Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria (12). Delirium incidence was 19.5% and 14.5% in the haloperidol and placebo groups respectively (Odds Ratio 1.43 95%CI: 0.72-2.78). There was no statistically significant difference in the secondary outcomes of delirium severity or duration; but there was significant uncertainty around these outcomes due to the high volume (over 50%) of missing delirium severity data.

The major methodological limitation of this study is under-powering, a problem that plagues many delirium studies. Sample size was based on an estimate for an absolute risk reduction (ARR) of 10% - this is higher than pooled estimates of treatment effect from trials of multicomponent delirium prevention interventions - ARR 6.6% (Number Needed to Treat (NNT) =15) (5). Due to problems with recruitment, the achieved sample size was 63% of the target of 390 patients, resulting in actual power of 59%. Under-powering increases the risk of a Type 2 error of failing to detect an effect of the intervention and failing to reject the null hypothesis (accepting a false negative). Pooling of results with comparable studies in meta-analysis can help to combat this but small studies are associated with inflated effect sizes (Type 2 error or publication bias) (13) which can result in heterogeneity and uncertainty in both the size and direction of any effect. Analysis of random effects can help to explain statistical heterogeneity (14) .

Delirium ascertainment is difficult and there is a degree of subjectivity with existing assessment tools. Clinician assessment for delirium against DSM criteria (as in the current study) is the gold-standard for delirium ascertainment – however, only participants scoring positively on the DOSS were assessed in this way. The DOSS has high sensitivity (90%) and specificity (91%) in general medical patients, with very low false negative rates (high negative predictive value) so this approach is unlikely to have adversely affected delirium detection (15).

The Cochrane Review of interventions for preventing of delirium in hospitalised non-ICU patients included two randomized controlled trials investigating haloperidol (pooled n=260) against placebo (pooled n=256) for delirium prevention (5). A pooled relative risk of 1.05 (95%CI 0.69-1.60) for prevention of incident delirium was reported. The trends to effect in were in opposite directions, and wide confidence limits indicate the uncertainty. Addition of the current study is unlikely to increase confidence in the role of haloperidol in the prevention of delirium due to uncertainty in the result (wide confidence limits).

Delirium research is difficult. It is a heterogeneous condition, ascertainment is imperfect and to a degree, subjective. The underlying pathological mechanisms and how these relate to subtypes of aetiology (toxic, infection, neurological injury, drugs or alcohol), setting (intensive care, surgical, medical, community), and phenomenology (hypoactive, hyperactive and mixed) are under-researched and currently not well described or understood. The current paradigm is that delirium represents a single condition, rather than that a number of conditions (or neurochemical disturbances) sharing a common presentation, but we should continue to question this in our endeavour better to understand the complexities of the delirium syndrome.

Future research needs to focus on developing and testing hypotheses of plausible pathways that are likely to lead to viable biomarkers and drug targets. This is a shift from the current status quo and requires conversations and joined up working between laboratory, basic science, pharmacology and clinical researchers. A better understanding of these issues is essential in order for the delirium research agenda to progress.

The ongoing large PRODEO randomised controlled trial (16) may help to clarify the efficacy of haloperidol for prevention of delirium in patients at high risk of delirium undergoing elective or emergency surgery, although questions of generalizability to patients outside surgical settings will remain. In the meantime, we should focus our efforts on implementation of multicomponent delirium prevention interventions whilst we work to build the evidence base in the basic science to support future delirium drug trials.

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