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Doing Damage in Delirium: The Hazards of Antipsychotic Treatment in Elderly Persons

Sharon K. Inouye, M.D., MPH[1,3], **Edward R. Marcantonio, M.D., SM**[1,3], and **Eran D. Metzger, M.D.**[2,4]

[1]Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

[2]Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

[3]Aging Brain Center, Institute for Aging Research,, Hebrew SeniorLife, Boston, MA

[4]Division of Psychiatry, Hebrew SeniorLife, Boston, MA

Delirium is a complex and morbid condition for older persons, precisely at the interface of mental and physical health. As an acute state with prominent cognitive and behavioral abnormalities triggered by an underlying organic etiology, the appropriate and timely management of delirium demands the shared expertise of mental and physical health care professionals. Occurring in up to 50% of older persons during hospitalization, the diagnosis is often missed and is associated with strikingly poor outcomes including prolonged length of stay, sustained functional decline, dementia, institutionalization, death, and high healthcare costs estimated at $164 billion per year in the USA and € 182 billion per year in 18 European countries combined (1).

Delirium can be associated with behavioral manifestations such as agitation, inappropriate behaviors, delusions, and hallucinations--which can be distressing to patients and their families. Moreover, these symptoms can make patients difficult to care for, and provide a source of caregiver burden and stress for both healthcare workers and informal carers. Largely to address these behavioral symptoms, the field of delirium prevention and treatment has evolved to focus on clinical trials of various antipsychotic drugs (2,3). A recent search of PubMed indicates that the annual number of studies using antipsychotic

Corresponding Author: Sharon K. Inouye, M.D., MPH Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife; 1200 Centre Street; Boston, MA 02459 USA sharoninouye@hsl.harvard.edu (not for publication) Phone: (617) 971-5390; Fax (617) 971-5309.

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drugs for prevention or treatment of delirium has demonstrated a progressive 20-fold increase over 20 years, from 2 studies in 1990 to over 40 studies in 2013.

This increasing trend necessitates an urgent call for caution in the use of antipsychotic drugs for the management of delirious patients. The use of antipsychotics might be considered counterintuitive, since all of these drugs are known to cause confusion or delirium as an adverse effect. Yet, powerful incentives in our current healthcare system promote prescription of antipsychotics for delirious patients, and have led to the high use of these drugs. Antipsychotics may have appeal as a potential “quick fix”, as compared to nonpharmacologic approaches. However, clinicians may not fully realize that their quest to make patients more “manageable” and less “distressed” may result in worsened clinical outcomes. In essence, these drugs can be considered to be a form of “chemical restraints”, and the concern is that the use of antipsychotic drugs like haloperidol and atypical antipsychotics for delirium may often be “treating the providers” rather than serving the best interests of the patient. The marketing and promotion by the pharmaceutical industry for off-label use of antipsychotics for agitation in cognitively impaired patients may have also contributed to this surge in use for delirium (4).

Treatment with antipsychotics may be warranted for severe agitation endangering patient safety or for psychotic symptoms, such as hallucinations or delusions, causing severe distress. Even in these situations, antipsychotics should be prescribed in the lowest effective dose for the shortest possible duration, generally less than 1-2 days. The continued use of antipsychotic therapy should always be revaluated regularly, particularly at any transitions of care. It is important to stress that in some settings—such as, surgery, recovery room, and intensive care settings--sedating drugs may be required to assure patient safety and avoid interruption of essential medical therapies (e.g., mechanical ventilation, central lines or arterial catheters); thus, the bar must be set differently in these venues. However, there is widespread use of these drugs for delirium even outside of these settings.

Making recommendations for any treatment is contingent upon demonstrating that the benefits of the treatment clearly outweigh the potential harms. The putative justification for antipsychotics involves dopaminergic blockade, relating to hypothesized dopamine excess and acetylcholine deficiency in delirium (5). While there is evidence for this hypothesized pathophysiology based on case reports of delirium from anticholinergic drug poisoning and dopaminergic drug excess and from animal models, it is unclear whether this mechanism explains most cases of delirium (5). Antipsychotics have also been hypothesized to have central anti-inflammatory effects, which may provide benefit in delirium but direct evidence is lacking. Several high quality systematic reviews have concluded that there is insufficient evidence to justify the use of antipsychotics for prevention or treatment of delirium (1, 6-8). Many of the studies reviewed were limited by small sample sizes and high risk of bias (i.e., nonrandomized, nonblinded, or inadequate control groups). In addition, wide variations in pharmacology across the various antipsychotic agents used may have influenced the results for both efficacy and safety in previous clinical trials. From a previously published comprehensive systematic literature review, 7 high quality studies were identified (Reference 1 Appendix, 9)(Table): 4 had reduced delirium rates, 5 demonstrated no difference in any other clinical outcomes examined, and 1 had worsened clinical outcomes.

While modest impact on delirium symptoms was demonstrated in 4/7 studies, there was no consistent benefit for any other outcomes.

The unclear benefits of antipsychotics need to be balanced against the concern for serious harms by these drugs (10-12). Common side effects reflect anticholinergic activity and alpha-receptor blockade, such as confusion, cognitive and functional decline, sedation, hypotension, orthostasis, dizziness, falls, urinary incontinence, voiding problems, and increased risk of urinary infections. While anticholinergic effects of atypical antipsychotics are milder than with other major tranquilizers, they are still present and contribute to significant morbidity. Extrapyramidal effects include parkinsonism, dystonias, and oropharyngeal dysphagia leading to a marked increased risk of pneumonia (13). Increased risks have been demonstrated for potentially fatal complications including stroke, seizures, venous thromboembolism, QT-prolongation and ventricular arrhythmias (10, 14-16). The risk of sudden cardiac death is increased over 2.4-fold with both typical and atypical antipsychotic drugs (15). Neuroleptic malignant syndrome is a rare but potentially fatal syndrome that has been associated with all classes of antipsychotic medications (17). While the risks increase with the dose and duration of treatment, even short-term treatment (10 weeks or less) has been associated with a 70% increased risk of mortality in older patients with dementia (18). Another important harm is the potential for inadvertent chronic administration of antipsychotics following inpatient initiation during an episode of delirium. A recent study showed that of 59 patients newly receiving antipsychotics during an episode of delirium, at least 33% continued on these drugs after hospital discharge without a clear indication (19). Finally, many patients with delirium have underlying dementia, and the risks of antipsychotic treatment, including death, are substantially increased in patients with dementia (11,18). These substantial risks sway the benefit: risk equation against treatment with antipsychotics for the off-label use of delirium.

Another important limitation of prior studies of antipsychotics in delirium are the outcome measures used (1). Unfortunately, all current delirium severity measures tend to overweight hyperactive symptoms (e.g., agitation, hallucinations); thus, patients with hyperactive delirium tend to receive higher severity scores. After antipsychotic treatment, the delirium severity score may be reduced, which the trialists may conclude demonstrates “treatment success”. However, in reality, these patients may have been converted to a hypoactive delirium which is missed, or the score may be reduced because of the bias in the severity measures (1,20). The issue of mis-measurement likely accounts for the worsened clinical outcomes in the 2 studies mentioned previously and the lack of any improvement in clinical outcomes in the other 5 studies. Thus, all of these prior studies need to be interpreted with caution. Development of improved delirium severity measures that focus more on the key symptoms of delirium such as attentional deficits rather than behavioral disorders is a critical area to be addressed to advance the field.

What are the alternatives to antipsychotic treatment? First and foremost, the clinician must address reversible contributors to delirium. Too often, this crucial step is neglected when the focus is on pharmacological treatment. Without assiduous attention to this key step, the patient will not improve. Next, removal or reduction of psychoactive drugs, particularly sedating and anticholinergic agents, should be considered in every patient. Finally, non-

pharmacologic multi-component intervention strategies have had demonstrated effectiveness for prevention and management of agitated patients without the use of physical or chemical restraints. The Hospital Elder Life Program (HELP)(21) and other multicomponent risk factor interventions for delirium have demonstrated effectiveness for prevention and management of delirious patients (22 and summarized in Reference 1-Appendix) through the use of nonpharmacologic intervention strategies (including mobilization, sleep enhancement, orientation, therapeutic activities, and environmental modifications) by trained volunteers and a geriatric interdisciplinary team. Delirium rooms (23) have also demonstrated promise for management of agitated delirious patients. While these multicomponent interventions may be more labor-intensive than simply prescribing a medication, their benefit: risk ratio is highly favorable, and cost-effectiveness has been demonstrated for HELP (24-25).

Current evidence does not support the use of antipsychotics for prevention or treatment of delirium. While more rigorous trials may shed new light in the future, the evidence for benefit is inconsistent or lacking in present studies. The risk of bias in outcome measurement of delirium incidence and severity is large across previous treatment trials; thus, their results must be interpreted with caution. Moreover, these trials have failed to demonstrate an improvement in other clinical outcomes closely associated with delirium. Finally, the risk of harm from antipsychotics including fatal complications is substantial in the older population. On balance, for the population as a whole, the risks clearly outweigh the benefits of treatment with antipsychotics. Treatment should thus be reserved only for the small proportion of patients with severe agitation and distress that pose a substantial risk of harm or of interruption of essential medical therapy.

What would it take to reduce use of antipsychotics for delirium? Given their widespread use, largescale efforts would be required, such as those being used to decrease antipsychotic use in nursing homes (See http://www.cms.gov/Outreach-and-Education/Outreach/NPC/National-Provider-Calls-and-Events-Items/2013-11-25-NPC-Dementia-Care.html). Such efforts should include comprehensive multi-media training of all healthcare professionals and awareness campaigns about the hazards of antipsychotic drugs for older persons. Incentives against prescribing will be required to have a true impact. Strategies might target physician order entry systems, such as safety screening questions before allowing prescription of an antipsychotic, or implementation of single or 24 hour dose limits for frail elders. System-wide strategies might include publicly posting antipsychotic prescribing rates in the elderly by hospital (e.g., Hospital Compare website), scrutiny of prescribing rates by accrediting organizations, and other quality improvement initiatives.

First, do no harm

As William Osler states, “One of the first duties of the physician is to educate the masses [patients, families, caregivers, nurses] not to take medicine”…in this case, not to use antipsychotics for delirium. The prevention and management of delirium must focus on approaches that address underlying causes and manage behavior disturbances nonpharmacologically in order to enhance recovery, maximize functional status, and

improve clinical outcomes. Certainly in the case of delirium, antipsychotic drugs are unlikely to be the answer.

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Table

Drug Trials for Prevention and Treatment of Delirium*

Author, Yr	Type	N, Study Population	Intervention/ Control	Study Results	Jadad Score †
Page 2013	P,T	141 ICU patients	Haloperidol/ placebo	No difference in delirium-free or coma-free days. No difference in mortality.	6
Hakim 2012	T	101 cardiac surgery 65+	Risperidone/ placebo	Lower delirium rate. No difference in LOS in ICU or hospital.	6
Wang 2012	P	457 noncardiac surgery/ICU patients 65+	Haloperidol/ placebo	Reduced incidence of delirium. No difference in LOS, complications, or mortality	6
Girard 2010	T	101 ICU patients	Haloperidol/ ziprasidone/ placebo	No difference in delirium-free or coma-free days. No difference in mortality	6
Larsen 2010	P	400 knee- or hip-replacement	Olanzapine/ placebo	Reduced incidence of delirium, but greater duration and severity in olanzapine	6
Prakanrattana 2007	P	126 cardiac surgery	Risperidone /placebo	Lower incidence of delirium. No difference in LOS, ICU days, or complications	6
Kalisvaart 2005	P	430 hip-surgery 70+	Haloperidol/ placebo	No difference in delirium; but decreased duration and severity; decreased LOS	6

*Full reference citations available on request. ICU= LOS: length of stay; N=number; P=Prevention Trial; T=Treatment Trial.

†The modified Jadad score (6 points) included: randomization or balanced allocation (1 point); description of method for balanced allocation (1); double blinding (1); description of double-blinding (1); description of withdrawals/dropouts (1); sample size ≥ 100 (1)