

## Delirium: Treatment and Prevention (Part 2)

KALYA VARDI, MD; COLIN J. HARRINGTON, MD

### ABSTRACT

Delirium management begins with non-pharmacologic interventions and treatment of the underlying causes. There are no FDA-approved medications for delirium-related psychosis and agitation, although numerous agents have been studied. Small sample size, narrow inclusion criteria, lack of placebo controls and variable methodologies limit the generalizability of findings to date. Studies and expert guidelines support the use of antipsychotics for delirium-related psychosis and agitation, and demonstrate comparable efficacy and safety between first- and second-generation agents. Mounting evidence also suggests that antipsychotics and dexmedetomidine are effective in preventing delirium in surgical and mechanically-ventilated patients, respectively.

**KEYWORDS:** delirium, encephalopathy, cognitive disorder, agitation

### INTRODUCTION

Delirium management begins with evaluation and treatment of its causes, discontinuation of potential offending agents, and institution of non-pharmacologic strategies to limit its incidence, course and complications. Pharmacologic treatment is typically reserved for neurobehavioral symptoms of agitation and psychosis that are unresponsive to these primary interventions. Despite its high prevalence and association with multiple adverse outcomes, there are no FDA-approved treatments for delirium.

Studies of delirium management have explored both treatment and prevention, have been conducted in general medical-surgical patients and in critically ill, intensive care unit (ICU) populations, and have included both pharmacologic and non-pharmacologic interventions. Unfortunately, small sample size, narrow inclusion criteria, lack of placebo controls, and variable methodologies limit the generalizability of findings to date.

Numerous agents have been studied for delirium management including antipsychotics, benzodiazepines, cholinesterase inhibitors and other pro-cholinergic drugs, ketamine, and, more recently, dexmedetomidine. Published guidelines from numerous subspecialty societies and recent meta-analyses recommend haloperidol and other antipsychotic

agents for the treatment of delirium.<sup>1,2</sup> Based on these and other consensus statements, antipsychotic agents remain the treatment of choice for delirium and related agitation.

### NON-PHARMACOLOGIC INTERVENTIONS

The landmark study by Inouye et al tested a multi-disciplinary protocol of non-pharmacologic interventions to reduce delirium incidence, duration and severity in 852 elderly patients admitted to the general medical service of an academic hospital.<sup>3</sup> The protocol consisted of both global interventions and targeted interventions for patients with specific risk factors. Interventions included early mobilization, noise reduction and scheduling adjustments to minimize sleep disruption, early recognition and treatment of dehydration, orientation boards and frequent verbal reorientation for patients with cognitive impairment, and communication aids for patients with visual and hearing impairment. The incidence of delirium was 40% lower in the intervention group compared with the control group. The total number of days spent in delirium was also significantly lower in the intervention group. Zaubler et al replicated these results and reported \$841,000 in cost savings over 9 months in a community hospital setting.<sup>4</sup> These protocols are considered the standard of care and have been put in place at institutions across the country. Similar non-pharmacologic interventions have been designed and implemented by the Brown-based Geriatric Medicine Program, and form the basis of the Close Observation Medical Unit (COMU) and other elder-care protocols at Rhode Island Hospital and The Miriam Hospital, respectively (L. McNicoll, personal communication, July 2012).

### PHARMACOLOGIC INTERVENTIONS – TREATMENT AND PREVENTION

#### Overview

First generation antipsychotics (FGA), such as haloperidol, are the mainstay for treating the neurobehavioral symptoms of delirium.<sup>1,5,6</sup> Their utility is thought to derive from dopaminergic blockade, based on the hypothesis that dopaminergic hyperactivity and cholinergic deficiency contribute to the onset and persistence of delirium. For this reason, cholinesterase inhibitors have also been tried with mixed results.<sup>6</sup> Haloperidol has minimal hemodynamic side effects and

remains the best studied and most recommended treatment for delirium-related agitation. Haloperidol can be administered orally, intramuscularly (IM) or intravenously (IV), has a wide therapeutic window, and can be titrated across a broad dose range, from 0.5 mg as needed to 10 mg hourly, with onset of action between 30-60 minutes for the IV and IM routes of administration. Peak serum concentrations occur 2-6 hours after oral administration. There are case reports of safe and effective haloperidol administration up to 500 mg per day.<sup>5</sup> Intravenous and IM forms of haloperidol are particularly helpful in uncooperative patients and in critically ill patients where gastrointestinal absorption is unreliable. Numerous reports suggest that IV administration is associated with less risk of extrapyramidal symptoms (EPS).<sup>5</sup> Emerging data suggests that, in addition to its anti-dopaminergic action, haloperidol may also counter delirium by decreasing oxidative stress and inflammation via  $\sigma$ -1 receptor blockade and interleukin-1 antagonism.<sup>6</sup>

There is a literature supporting the use of second-generation antipsychotics (SGAs) in the treatment of delirium-related agitation and psychosis.<sup>2,5-9</sup> SGAs studied to date include risperidone,<sup>10,11</sup> quetiapine,<sup>12</sup> olanzapine,<sup>9,13</sup> ziprasidone,<sup>5</sup> and aripiprazole.<sup>5</sup> The main advantage of the SGAs over haloperidol is their relatively reduced risk of EPS, which is particularly relevant in patients with parkinsonian syndromes such as dementia with Lewy bodies (DLB) and idiopathic Parkinson's disease (PD). Quetiapine is least likely to produce or exacerbate EPS and is the agent of choice in treating agitation and psychosis in parkinsonian patients. Unlike haloperidol, none of the SGAs are available IV. Olanzapine, ziprasidone, and aripiprazole can be administered in immediate-release intramuscular forms and are indicated when the oral route is unavailable and haloperidol is contraindicated. Risperidone and paliperidone are available in long-acting intramuscular depot formulations which are utilized in the treatment of patients with chronic psychotic illnesses, but are not indicated in delirium.

The FDA issued "black box" warnings in April 2005 and June 2008 regarding the use of antipsychotic agents in the elderly. These warnings were based upon evidence of increased cerebrovascular events and all-cause mortality in studies of extended courses of antipsychotic treatment in elderly, demented nursing home patients.<sup>14</sup> The relevance of these findings and warnings to the short-term use of these agents in patients with delirium is unclear. Given the high prevalence of co-morbid dementia in delirium patients, these warnings should be taken into consideration when weighing the potential risks and benefits of brief antipsychotic treatment against those of untreated delirium.

Haloperidol and all SGAs carry a risk of QTc prolongation (QTP) and QTP is the best predictor of torsade de pointes (TdP), a malignant ventricular dysrhythmia. The QT prolonging effects of antipsychotic and other agents are catalogued at [www.torsades.org](http://www.torsades.org). Low-dose oral haloperidol has minimal QT prolonging effects. Thioridazine, ziprasidone

and high-dose IV haloperidol have the most significant QT prolonging effects of the antipsychotic agents. Although the degree of QTP and absolute risk of TdP associated with these agents is small, most guidelines advise caution when using IV haloperidol in patients with risk factors for QTP or TdP (Table 1). The absolute risk of TdP for IV haloperidol has been estimated at 0.27%.<sup>5</sup>

**Table 1. Assessing and Monitoring Risk for Drug-Induced QTc Prolongation (QTP)**

<p><b>Risk Factors for QTP:</b></p> <ul style="list-style-type: none"> <li>• Advanced cardiac disease</li> <li>• Known history of long-QT syndrome</li> <li>• Baseline QTc &gt; 450 msec</li> <li>• Hypokalemia</li> <li>• Hypomagnesemia</li> <li>• Concomitant use of other QTc prolonging agents</li> </ul>
<p><b>Prior to Initiating a QTc Prolonging Drug:</b></p> <ul style="list-style-type: none"> <li>• Obtain electrocardiogram to measure baseline QTc interval</li> <li>• Obtain serum potassium and magnesium levels</li> <li>• Correct any electrolyte abnormalities</li> <li>• Review medication list for QTc-related interactions</li> </ul>
<p><b>After Initiating a QTc Prolonging Drug:</b></p> <ul style="list-style-type: none"> <li>• Repeat electrocardiogram at regular intervals (typically once daily)</li> </ul>

Dexmedetomidine is a highly selective, centrally-acting alpha-2 agonist with sedative, analgesic and anxiolytic properties, and has been studied for both prevention of delirium and treatment of delirium-related agitation in ICU patients. Trials comparing dexmedetomidine to benzodiazepine and opioid ICU sedation protocols have demonstrated its efficacy, safety and favorable side effect profile.<sup>15-19</sup> Unlike most other sedatives employed in the ICU, dexmedetomidine is not associated with significant respiratory depression; however, hypotension and bradycardia can complicate its use, especially at high infusion rates.<sup>6,15-19</sup> Multiple studies have reported decreased opiate requirements in ICU and post-operative patients sedated with dexmedetomidine.<sup>5</sup> Reduced opioid use likely contributes to the lower incidence of delirium observed in dexmedetomidine-treated patients. Dexmedetomidine is also thought to have mild cholinergic activity which may favorably affect the sleep-wake cycle.<sup>5</sup>

Benzodiazepines are potentially deliriogenic. Except for cases of alcohol and sedative-hypnotic withdrawal where they are the treatment of choice, benzodiazepines are not considered first-line agents in the treatment of delirium-related agitation.<sup>20</sup> *Adjunctive* use of benzodiazepines is appropriate in cases of agitation related to certain toxidromes and neuroleptic-malignant syndrome, or when delirium is complicated by catatonia or severe EPS that limit the use of antipsychotic agents.

The existing literature is summarized below with special attention to differences between *general medical-surgical* patients versus *ICU* patients. Outcome measures vary across these studies and include delirium incidence, severity and duration, length of hospitalization, length of time in the ICU, number of ventilator dependent days, and disposition to home versus other medical facilities or institutional settings.

Typical teaching recommends the use of antipsychotic agents for the treatment of delirium-related psychosis and agitation but not for the delirium syndrome proper. Animal studies suggest that dopaminergic mechanisms play a role in the development of delirium irrespective of the presence or absence of agitated behavior. Additionally, recent studies and personal accounts suggest that a significant proportion of non-agitated, "hypoactive" delirium patients experience distressing psychotic symptoms and that these frightening symptoms may drive the development of a post-traumatic stress disorder (PTSD)-like syndrome.<sup>21,22</sup> Taken together, these observations may argue for more liberal use of dopamine-blocking agents in the treatment of delirium, even in the absence of problem behaviors.

## TREATMENT STUDIES

### General Medical and Surgical Patients

Multiple case reports and small, open-label trials suggest that SGAs (including risperidone, quetiapine, olanzapine, aripiprazole and ziprasidone) are effective and safe in the treatment of delirium.<sup>5,9,13</sup> Several single-blind, randomized trials comparing SGAs to haloperidol for the treatment of delirium found no significant differences between the two interventions in treatment outcomes or adverse effects.<sup>5</sup> One double-blind RCT of risperidone versus haloperidol in 28 delirious patients reported comparable improvement across groups.<sup>10</sup> A 2007 Cochrane review of antipsychotic use in delirium included a meta-analysis of haloperidol, olanzapine, risperidone and placebo treatment studies, and concluded that (1) haloperidol does not significantly reduce delirium *incidence* compared with placebo, (2) low-dose haloperidol reduces delirium severity and duration in post-operative patients, (3) low-dose haloperidol and the SGAs have similar efficacy and EPS incidence, and (4) higher dose haloperidol is associated with more severe EPS.<sup>8</sup>

### ICU Patients

In the MIND study, which evaluated prevention and treatment, 101 mechanically-ventilated ICU patients were randomized to receive oral haloperidol, oral ziprasidone, or placebo for up to 14 days according to a protocol which allowed for dose adjustments based on delirium severity, level of sedation and side effects.<sup>23</sup> Neither agent significantly reduced the duration of delirium, although the study was most likely underpowered due to small sample size, inclusion of patients without delirium at baseline, and open-label IV haloperidol use across groups. There was no difference in

duration of coma between groups, a measure included due to concern that the sedating effects of antipsychotics may prolong coma. Rates of EPS, including akathisia, were comparable across groups. Extrapyramidal signs and symptoms were assessed by physical exam. Akathisia in particular, could only be assessed when patients were neither comatose nor delirious, and could participate in the assessment. A 2013 international study used similar methods to compare IV haloperidol to placebo for prevention and treatment of delirium in mechanically-ventilated patients, and found no significant difference between groups in duration of delirium.<sup>24</sup>

Devlin et al randomized 36 delirious, ICU patients to receive oral quetiapine or placebo.<sup>12</sup> Treatment with quetiapine was associated with shorter total duration of delirium, shorter time to first resolution of delirium, and less hours of agitation compared with placebo. Significantly more adverse effects were reported in the quetiapine group, especially sedation; however, no EPS or QTP were observed.

In a small, open-label trial, mechanically-ventilated ICU patients with severe agitation secondary to delirium were randomized to receive a continuous infusion of either dexmedetomidine or haloperidol.<sup>15</sup> The dexmedetomidine group spent more time with minimal or no delirium symptoms, less time intubated, less time in the ICU and less time in mechanical restraints. Three patients receiving haloperidol could not be extubated and underwent tracheostomy, compared with none in the dexmedetomidine group. Haloperidol was discontinued early in one patient due to QTP.

A qualitative meta-analysis of antipsychotic use for delirium in ICU patients reviewed three studies including the MIND and Devlin trials and a study by Skrobik et al of 73 delirious ICU patients randomized to oral olanzapine or haloperidol.<sup>9</sup> Evidence was strongest for the beneficial effects of quetiapine in the treatment of delirium. Guidelines from the American College of Critical Care Medicine (ACCM) report similar evidence for quetiapine and other SGAs in comparison to haloperidol in reducing the duration of delirium in ICU patients.<sup>2,9</sup>

An RCT of rivastigmine versus placebo as adjunct to haloperidol for ICU delirium was stopped early due to increased mortality in the rivastigmine group.<sup>25</sup> The median duration of delirium, severity of delirium, length of ICU stay, and cumulative doses of *as needed* haloperidol, lorazepam and propofol were all higher in the rivastigmine group. The dosing schedule for rivastigmine was different from the regimen used in Alzheimer's disease, with increases allowed every 2-3 days based on the assumption that correction of the functional cholinergic deficit of delirium would be more rapid than that of chronic dementia.<sup>25</sup> The ACCM advises against using rivastigmine for delirium in adult ICU patients.<sup>2</sup>

## PREVENTION STUDIES

### General Medical and Surgical Patients

At least three studies have examined prophylactic anti-

psychotic use in patients undergoing orthopedic or gastrointestinal surgery. In a double-blind study, Kalisvaart et al randomized 430 hip surgery patients to receive oral haloperidol or placebo from admission until the third post-operative day.<sup>26</sup> The *incidence* of delirium was similar between groups; however, delirium episodes were shorter and less severe in the haloperidol group. Kaneko et al randomized 78 gastrointestinal surgery patients to receive haloperidol or normal saline IV on post-operative days one through five.<sup>7</sup> The incidence, severity and duration of delirium were significantly lower in the haloperidol group. In a double-blind study, Larsen et al randomized 400 patients undergoing hip or knee replacement surgery to receive one dose of olanzapine or placebo immediately pre- and post-operatively.<sup>13</sup> Delirium incidence was significantly lower in the olanzapine group (14.3% vs. 40.2%,  $p < 0.0001$ ) and more patients in the olanzapine group were discharged to home. Notably, when delirium did occur in the olanzapine group, it lasted longer and was more severe. The latter findings were attributed to the unexpected development of alcohol withdrawal in five of the 28 patients in the treatment group versus none in the control group.

### ICU Patients

Two studies have examined prophylactic antipsychotic use in postoperative ICU patients. Prakanrattana et al randomized 126 cardiac surgery patients to receive a single dose of risperidone or placebo postoperatively.<sup>11</sup> Delirium incidence was significantly lower in the risperidone group. Wang et al randomized 457 cardiac surgery patients to receive a continuous infusion of either haloperidol or normal saline postoperatively.<sup>27</sup> Haloperidol treatment was associated with a lower 7-day incidence of delirium, longer time to delirium onset, and a greater number of delirium free-days. A recent meta-analysis of studies examining delirium prevention in general and ICU surgical patients calculated a relative risk of 0.5 for developing delirium in patients receiving prophylactic antipsychotic medication compared with placebo.<sup>7</sup>

Three RCTs have examined the incidence of delirium among ICU patients sedated with dexmedetomidine versus benzodiazepines or opioids. The MENDS trial randomized 106 mechanically-ventilated ICU patients to sedation with dexmedetomidine or lorazepam.<sup>16</sup> The number of days alive without coma or delirium was significantly higher in the dexmedetomidine group. Maldonado et al randomized 118 mechanically-ventilated, cardiac surgery patients to dexmedetomidine, propofol or midazolam sedation protocols.<sup>17</sup> Delirium incidence was significantly lower in the dexmedetomidine group but there were no significant differences in length of ICU or hospital stay. In the DEXCOM study, 306 cardiac surgery patients were randomized to either dexmedetomidine or morphine for sedation and analgesia on admission to the ICU.<sup>18</sup> Delirium incidence was comparable, but dexmedetomidine-treated patients spent three fewer days in delirium, were extubated earlier, experienced less hypotension

and required less norepinephrine. Dexmedetomidine use was associated with significantly higher incidence of bradycardia. Dexmedetomidine is an expensive drug, but a recent cost analysis comparing it to midazolam for sedation in mechanically-ventilated ICU patients reported a median savings of \$9,679 per ICU stay in dexmedetomidine treated patients.<sup>19</sup>

Two placebo controlled studies reported no benefit of cholinesterase inhibitors for delirium prevention in surgical ICU patients.<sup>6</sup> In contrast, ketamine administered during anesthesia induction was associated with a lower incidence of postoperative delirium compared to placebo in cardiac surgery patients (3% versus 31%).<sup>28</sup>

### CONCLUSION

Studies and expert guidelines support the use of anti-psychotics for the *treatment* of delirium-related psychosis and agitation. First- and second-generation agents have demonstrated comparable efficacy and safety. Non-pharmacologic interventions significantly reduce delirium incidence, duration and severity. There is growing evidence that antipsychotics and dexmedetomidine are effective in *preventing* delirium in surgical and mechanically-ventilated patients, respectively.

### References

1. American Psychiatric Association: Practice guideline for the treatment of patients with delirium. *Am J Psychiatry*. 1999;156(5 suppl):1–20.
2. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263–306.
3. Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340(9):669–76.
4. Zaubler TS, Murphy K, Rizzuto L, et al. Quality improvement and cost savings with multicomponent delirium interventions: replication of the Hospital Elder Life Program in a community hospital. *Psychosomatics*. 2013;54(3):219–26.
5. Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. *Crit Care Clin*. 2008;24(4):657–722, vii.
6. Bledowski J, Trutia A. A review of pharmacologic management and prevention strategies for delirium in the intensive care unit. *Psychosomatics*. 2012;53(3):203–11.
7. Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. *Psychosomatics*. 2013;54(2):124–31.
8. Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. *Cochrane Database Syst Rev*. 2007;(2):CD005594.
9. Devlin JW, Skrobik Y. Antipsychotics for the prevention and treatment of delirium in the intensive care unit: what is their role? *Harv Rev Psychiatry*. 2011;19(2):59–67.
10. Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. *Psychosomatics*. 2004;45(4):297–301.
11. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesth Intensive Care*. 2007;35(5):714–9.

12. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med*. 2010;38(2):419-27.
13. Larsen KA, Kelly SE, Stern TA, et al. Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. *Psychosomatics*. 2010;51(5):409-18.
14. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafety-InformationforPatientsandProviders/ucm124830.htm>. Accessed January 22, 2014.
15. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomized open-label trial. *Crit Care*. 2009;13(3):R75.
16. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. 2007;298(22):2644-53.
17. Maldonado JR, Wysong A, Van der starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*. 2009;50(3):206-17.
18. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine Compared to Morphine-DEXCOM Study). *Anesthesiology*. 2009;111(5):1075-84.
19. Dasta JF, Kane-Gill SL, Pencina M, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. *Crit Care Med*. 2010;38(2):497-503.
20. Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med*. 2004;164(13):1405-12.
21. Misak CJ. The critical care experience: a patient's view. *Am J Respir Crit Care Med*. 2004;170(4):357-9.
22. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Crit Care Med*. 2001;29(3):573-80.
23. Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. *Crit Care Med*. 2010;38(2):428-37.
24. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2013;1(7):515-23.
25. van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet*. 2010;376(9755):1829-37.
26. Kalisvaart KJ, De Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc*. 2005;53(10):1658-66.
27. Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial\*. *Crit Care Med*. 2012;40(3):731-9.
28. Hudetz JA, Patterson KM, Iqbal Z, et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 2009;23(5):651-7.

## Authors

Kalya Vardi, MD, is a Psychiatry Resident, General Psychiatry Residency Training Program at Butler Hospital and the Alpert Medical School of Brown University.

Colin J. Harrington, MD, is Director, Consultation Psychiatry and Neuropsychiatry Education, Rhode Island Hospital and Associate Professor (clinical), Clinician Educator, Departments of Psychiatry and Medicine at the Alpert Medical School of Brown University.

## Correspondence

Colin J. Harrington, MD  
Rhode Island Hospital, APC 9  
593 Eddy St.  
Providence, RI 02903  
401-444-5480  
Fax 401-444-3492

[Colin\\_Harrington@Brown.Edu](mailto:Colin_Harrington@Brown.Edu)