ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF DELIRIUM

Vaxevanis A, Syngelakis M, Vidalis A

Psychiatric Sector, Psychiatric Department, HIPPOCRATIO General Hospital, Thessaloniki, Greece

Atypical antipsychotic agents have been recently used in the clinical practice for the treatment of delirium and the existing data have been shown atypicals to be effective and safe. Conversely, information regarding the efficacy and safety comes mainly from open trials in small non-representative samples; randomized controlled trials are extremely few. The existing literature lacks the required scientific evidence, however a lot of data provide the rationale for prospective large-scale double-blind studies.

Delirium is an acute confusional state characterized by the fluctuating levels of consciousness and impairment in attention, cognition, perception, and behavior. There is evidence that the disturbance is caused by the direct physiological consequences of general medical conditions[1]. Conditions commonly associated with delirium are CNS disorders, metabolic disorders, cardiopulmonary disorders, systemic illness, postoperative state, medications and toxins...[2] The prevalence of delirium have been reported between 10%-30% in the hospitalized medically ill to more than 80% of patients with terminal illness[2-4].
The duration of symptoms range from less than one week to more than two months. Typically the symptoms of delirium are resolved within 10-12 days. The majority of the patients recover fully. Delirium may progress to stupor, coma, seizures or death particularly if untreated. Full recovery is less likely in the elderly. Delirium, particularly in the elderly, is associated with significant morbidity and an increased mortality rate; however delirium remains an underrecognized, underdiagnosed and undertreated mental disorder[2].

The management of delirium involves two key aspects: First the treatment of the underlying pathological condition and second the symptomatic and supportive therapy.
Antipsychotics have been the medication of choice[2]. Haloperidol is most frequently used because it has no active metabolites, few or no anticholinergic side effects, minimal cardiovascular side effects and a relatively small likelihood of causing sedation[2]. However haloperidol is frequently associated with extrapyramidal side effects (EPS) -including laryngeal dystonia and dysphagia[5]; intravenous administration is maybe associated with less EPS; elderly and patients with comorbid conditions not-rarely observed in the medical setting (Parkinson disease, Lewy-body dementia, basal ganglia strokes, AIDS...) are more sensitive to EPS; Neuroleptic malignant syndrome and increased vulnerability to QT prolongation are also problematic side effects of the haloperidol[2,5].
The use of haloperidol is primarily based in accumulated clinical wisdom; research is limited. Breitbart et al (1996)[6] in a randomized controlled trial (RCT) with delirious AIDS patients concluded that low-dose neuroleptics (haloperidol or chlorpromazine) resulted in a significant improvement in the symptoms of delirium; treatment was associated with an extremely low prevalence of EPS; lorazepam alone was ineffective and associated with treatment-limiting adverse effects. Results of several open studies suggest that combined treatment (haloperidol plus lorazepam) is more efficacious; benzodiazepines maybe particular useful for antipsychotic side effects (anticholineric, EPS) or when there is a need to raise the seizure threshold[2].

Recently several papers have been published reporting the use of the atypical antipsychotic agents risperidone, olanzapine, quetiapine, and ziprasidone. Atypicals have been used in clinical practice for the treatment of delirium as they are principally associated with a lower risk of EPS. Second generation antipsychotics have been also used in delirium resistant to haloperidol treatment (Vidalis et al, unpublished data).
To our knowledge, the first report on the use of atypicals in delirium was a retrospective study of 103 elderly patients with dementia or delirium. Robertsson et al (1996)[7] treated the patients with remoxipride and reported that when psychomotor hyperactivity was the dominant problem a good effect was rated in 81% of the patients, while side effects were few and mild. Remoxipride has been world-wide withdrawn due to safety reasons.

Sipahimalani & Masand[8] and Sipahimalani et al (1997)[9] reported at least some improvement in 8 out of 11 delirious patients in which they had administered risperidone. Dosages were started at 0.5mg bid, and were gradually increased every 3-4 days (range: 1-4mg/d). One patient showed signs of EPS and one experienced dizziness. Azuma et al (1998)[10] reported a case of delirium developed during the treatment for parkinson's disease in an 69y old patient; restlessness and excitement were resolved after administration of risperidone 1mg/d. Ravona-Springer et al (1998)[11] reported three elderly patients treated with risperidone; Lerner et al (2000)[12] also reported the treatment of three delirious patients; Nishimura et al (2003)[13] presented a case of delirium due to neuropsychiatric lupus erythematosus treated with risperidone; Temple (2003)[14] successfully managed by risperidone a delirium in traumatic brain injury.
Horikawa et al (2003)[15] conducted a preliminary open clinical

study on risperidone in 10 patients with delirium, at a dose of 1.7mg/d on average; one patient responded at a dose of 0.5mg/d. The treatment was effective in eight patients, however sleepiness (in three patients) and mild drug-induced parkinsonism (in one patient) were observed. Liu et al (2004)[16] retrospectively analyzed 41 delirious patients who received risperidone treatment and 36 patients who received haloperidol. Risperidone (mean dose 1.2±0.8 mg, range 0.5–4.0 mg) and haloperidol were both effective for treating hyperactive symptoms of delirium; the psychiatrists tended to recommend haloperidol for patients with severely hyperactive symptoms and risperidone for older patients and patients with moderate hyperactive symptoms; the patients on haloperidol needed much more anticholinergics. A 6-day clinical trial on risperidone was carried out in 10 medically-ill patients with delirium by Mitral et al (2004)[17]. They administered an initial dose of 0.5 mg bid, with additional doses on day 1, until Delirium Rating Scale (DRS) score was <13; dosage was then decreased by 50% (mean maintenance dose: 0.75mg/d). Their conclusion was that risperidone can improve cognitive and behavioral symptoms of delirium. Two patients discontinued because of sedation or hypotension. Parellada et al (2004)[18] conducted a prospective, multicenter, observational 7-day study in 67 patients with delirium. Response to the treatment was defined as a reduction in DRS score to <13 within 72 hours. Risperidone (mean dose 2.6±1.7mg at day 3) was effective in 90.6% of the patients; two patients (3.1%) experienced adverse events.
Hans & Kim (2004)[19] performed a double-blind comparative study; twenty-eight patients with delirium were randomly assigned to receive haloperidol or risperidone over a period of 7 days. The RCT showed no difference in the efficacy between the two groups.

Sipahimalani & Masand (1998)[20] reported an open study in which 11 delirious patients were treated with olanzapine (8.23.4mg/d, range 5-15mg/d) and 11 delirious control patients were treated with haloperidol (5.1±3.5mg/d, range 1.5-10mg/d). Five of the olanzapine patients showed significant improvement on DRS and none of the patients had side effects, whereas six of the control subjects showed improvement on the DRS but five had EPS or excessive sedation. Peak response time was similar in both groups. Passik & Cooper (1999)[21] successfully managed by olanzapine a complicated delirium, in which low doses of haloperidol were ineffective; Khouzam et al (1999)[22] reported three geriatric patients treated with olanzapine in the course of post-operative delirium.
Kim et al (2001)[23] conducted a trial of olanzapine in 20 patients with delirium (mean dose 5.9±1.5, max.dose 8.8±2.2 mg/d). The scores of DRS were significantly improved and no serious side effects were observed. Breitbart et al (2002)[24] held an open prospective clinical trial of olanzapine for the treatment of delirium in a sample of 79 hospitalized cancer patients. Fifty-seven (76%) completely recovered from their delirium on olanzapine therapy. No patients experienced EPS; however, 30% experienced sedation, which was not severe enough to interrupt treatment. Age >70y was a powerful predictor of poorer response to olanzapine treatment.
Skrobik et al (2004)[5] in a RCT compared safety and efficacy of olanzapine to haloperidol in a critical care setting. Clinical improvement was similar, whereas the use of haloperidol was associated with low scores on EPS testing. The authors concluded that olanzapine is maybe of particular interest in patients in whom haloperidol is contradicted.

Schwartz & Massand (2000)[25] retrospectively reviewed charts of 22 patients with delirium; eleven had been treated with quetiapine (average dose 211.4mg/d) and 11 with haloperidol (3.4mg/d). Authors reported that quetiapine was as effective as haloperidol but was better tolerated with a lower incidence of EPS. Torres et al (2001)[26] and Al-Samarrai et al (2003)[27] presented quetiapine for treatment of delirium in case reports. Kim et al (2003)[28], administered quetiapine (mean dose 94±23mg/d) to 12 elderly hospitalized delirium patients (mean age 74±7y). They reported that treatment was effective and safe in older patients with delirium. The DRS scores as well as the scores of the Mini-Mental State Examination and Clock Drawing test continued to improve throughout the 3-month study period. Sasaki et al (2003)[29] conducted an open-label flexible-dose study in 12 patients with delirium. The mean dose of quetiapine was 45±31mg/d. All patients achieved remission of delirium several days after and no EPS were detected. Pae et al (2003)[30] administered prospectively quetiapine in a pilot trial, in 22 patients; authors concluded that quetiapine could be a useful alternative agent to classical antipsychotics.

Leso & Schwartz (2002)[31] in a case-report found ziprasidone (100mg/d, po) to be effective in an AIDS patient with cryptococaal meningitis and electrolyte abnormalities for whom risperidone was stopped due to EPS. Young & Lujan (2004)[32] presented the use of intravenous ziprasidone to treat ICU-related delirium refractory to haloperidol treatment.

Tune et al (2001)[33] reported the preliminary results of a prospective investigation for the management of acute delirium in elderly patients with dementia. Twenty-seven patients received atypicals (risperidone, olanzapine or quetiapine), 9 received a standing dose of haloperidol, 7 prn haloperidol and 9 a combination of typical and atypical antipsychotics. Atypical antipsychotics were obviously superior to therapy with prn haloperidol and to combination therapy. Patients receiving haloperidol or combination antipsychotics showed a significant deterioration in EPS.

Novel antipsychotics are effective and well tolerated in common psychiatric disorders but they are not well studied in medically-ill patients. Second generation antipsychotics are not without side effects. Somnolence or dizziness are sometimes caused by atypicals use; quetiapine probably causes more sedation. Risperidone and olanzapine are associated with mild EPS, maybe dosage dependent. Olanzapine has mild anticholinergic adverse effects. Olanzapine and quetiapine

have an adverse effect on glucose regulation. Ziprasidone is associated with QT prolongation; a case of torsades de pointes caused by a small dose of risperidone in a cancer patient has been reported.35 Coadministration of benzodiazepines and atypicals may be associated with an increased incidence of syncope and respiratory depression; parenteral coadministration of olanzapine and benzodiazepine is precluded.

Recently (2003-4) safety warnings were issued by EMEA, as well as by the manufacturer of olanzapine (Eli Lilly) and the manufacturer of risperidone (Janssen); they refer to an increased risk of cerebrovascular adverse events and mortality rate due to the use of olanzapine or risperidone in elderly patients suffering from dementia[35,36].

Bergeron & Strobik (2004)[5] argue that besides the insufficient data to confirm any difference in the risk of death between antipsychotics, serious adverse events were found in long-term therapy which limits the comparison to the short-term drug treatment used in (ICU) delirium; anyway, identifying preexisting cardiovascular or cerebrovascular disease, conditions which predispose to higher EPS risk, patients at risk of hypotension and abnormal QT prolongation is essential prior to utilization of any antipsychotic.

The existing data have been shown that the newer atypical antipsychotics may have potential in the treatment of delirium and also have the added benefit of causing less dysphoria and akathisia[37]. On the other hand information regarding efficacy and risks comes mainly from case reports or open trials in small non-representative samples; sometimes authors use informal measures of delirium or delirium symptom severity; lack of control group is another serious methodological consideration. Scientific evidence is too limited to draw firm conclusions, while a lot of data provide the rationale for prospective RCTs.

In conclusion, atypicals may be a clinically efficacious and safe alternative in the treatment of delirium, especially when comorbid conditions raise concern about the side effects of the haloperidol. However the few clinical trials, the weak research methods and recent data regarding safety suggest that the literature lacks the required evidence-base; further double-blind, multicenter, large-scale studies to evaluate the safety and efficacy of new atypical antipsychotics in the treatment of delirium are warranted.

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV). Washington, DC: APA, 1994.
2. American Psychiatric Association: Practice Guideline for the Treatment of Patients with Delirium. Am J Psychiatry 1999; 156 (Suppl): 1-20.
3. Lipowski ZJ: Delirium (Acute confusional states). JAMA 1987; 258:1789-1792.
4. Cacaeni A, Grassi L. Delirium: Acute Confusional States in Palliative Medicine. New York : Oxford University Press, 2003
5. Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, Corbera K, Raymond S, Lund S, Jacobson P. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996; 153:231-7.
6. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004; 30:444-9. [Comment in: Intensive Care Med 2004; 30:1500; author reply 30:1501.]
7. Robertsson B, Karlsson I, Eriksson L, Olsson JO, Olofsson H, Jacobsson NO, Arnell G. An atypical neuroleptic drug in the treatment of behavioural disturbances and psychotic symptoms in elderly people. Dementia 1996; 7:142-6.
8. Sipahimalani A, Masand PS. Use of risperidone in delirium: case reports. Ann Clin Psychiatry 1997; 9:105-107.
9. Sipahimalani A, Sime R, Masand P. Treatment of delirium with risperidone. Int J Ger Psychopharmacol 1997; 1:24-26.
10. Azuma M, Kirime E, Ohta J, Sugimoto M, Iida J, Hanada M. A case of delirium developed during treatment for Parkinson's disease successfully treated with risperidone. The Journal of the Kyushu Neuropsychiatry Association 1998; 44(3,4):312-313.
11. Ravona-Springer R, Dolberg OT, Hirschmann S, Grunhaus L. Delirium in elderly patients treated with risperidone: a report of three cases. J Clin Psychopharmacol 1998; 18:171-2.
12. Lerner DM, Schuetz L, Holland S, Rubinow DR, Rosenstein DL. Low-dose risperidone for the irritable medically ill patient. Psychosomatics 2000; 41:1, 69-71.
13. Nishimura K, Omori M, Horikawa N, Tanaka E, Furuya T, Harigai M. Risperidone in the treatment of acute confusional state (delirium) due to neuropsychiatric lupus erythematosus: case report. Int J Psychiatry Med 2003; 33:299-303.
14. Temple MJ. Use of atypical anti-psychotics in the management of post-traumatic confusional states in traumatic brain injury. J R Army Med Corps 2003; 149:54-5.
15. Horikawa N, Yamazaki T, Miyamoto K, Kurosawa A, Oiso H, Matsumoto F, Nishimura K, Karasawa K, Takamatsu K. Treatment for delirium with risperidone: results of a prospective open trial with 10 patients. Gen Hosp Psychiatry 2003; 25:289-292.
16. Liu CY, Juang YY, Liang HY, Lin NC, Yeh EK. Efficacy of risperidone in treating the hyperactive symptoms of delirium. Int Clin Psychopharmacol 2004; 19:165-8.
17. Mittal D, Jimerson NA, Neely EP, Johnson WD, Kennedy RE, Torres RA, Nasrallah HA. Risperidone in the treatment of delirium: results from a prospective open-label trial. J Clin Psychiatry 2004; 65(5):662-7.
18. Parellada E, Baeza I, de Pablo J, Martinez G. Risperidone in the treatment of patients with delirium. J Clin Psychiatry 2004; 65:348-53.
19. Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics 2004; 45:297-301.
20. Sipahimalani A, Masand PS. Olanzapine in the treatment of delirium. Psychosomatics. 1998; 39:422-430.
21. Passik SD, Cooper M. Complicated delirium in a cancer patient

successfully treated with olanzapine. J Pain Symptom Manage 1999; 17:219–23.
22. Khouzam HR, Gazula K. Clinical experience with olanzapine in the course of post-operative delirium associated with psychosis in geriatric patients: A report of three cases. Int J Psych Clin Pract 2001; 5:63–68.
23. Kim KS, Pae CU, Chae JH, Bahk WM, Jun T. An open pilot trial of olanzapine for delirium in the Korean population. Psychiatry Clin Neurosci 2001; 55:515–9.
24. Breibart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics 2002; 43:175–182
25. Schwartz TL, Masand PS. Treatment of Delirium With Quetiapine. J Clin Psychiatry 2000; 2:10–12.
26. Torres R, Mittal D, Kennedy R. Use of quetiapine in delirium: case reports. Psychosomatics 2001; 42:347–9.
27. Al-Samarrai S, Dunn J, Newmark T, Gupta S. Quetiapine for treatment-resistant delirium. Psychosomatics 2003;44:350–1.
28. Kim KY, Bader GM, Kotlyar V, Gropper D. Treatment of delirium in older adults with quetiapine. J Geriatr Psychiatry Neurol 2003; 16:29–31
29. Sasaki Y, Matsuyama T, Inoue S, Sunami T, Inoue T, Denda K, Koyama T. A prospective open-label, flexible-dose study of quetiapine in the treatment of delirium. J Clin Psychiatry 2003; 64:1316–1321
30. Pae CU, Lee SJ, Lee CU, Lee C, Paik IH. A pilot trial of quetiapine for the treatment of patients with delirium. Hum Psychopharmacol 2004; 19:125–7.
31. Leso L, Schwartz TL. Ziprasidone treatment of delirium. Psychosomatics 2002; 43:61–2.
32. Young CC, Lujan E. Intravenous ziprasidone for the treatment of delirium in the intensive care unit. Anesthesiology 2004; 101:794–795
33. Tune L, Jewart D, Egeli S, Greene Y. Pharmacologic management of acute delirium: A naturalistic, prospective comparison of atypical antipsychotics and haloperidol, using average length of stay and EPS rating as outcome measurements (poster). American Psychiatric Association Institute on Psychiatric Services; Orlando, Florida; October 10–14, 2001.
34. Tune L. The role of antipsychotics in treating delirium. Curr Psychiatry Rep 2002; 4:209–12.
35. Tei Y, Morita T, Inoue S, Miyata H. Torsades de pointes caused by a small dose of risperidone in a terminally ill cancer patient. Psychosomatics 2004; 45:450–1.
36. European Agency for the Evaluation of Medicinal Products (EMEA). Public statement on the safety of olanzapine. http://www.emea.eu.int/pdfs/human/press/pus/0805604en.pdf
37. Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. CMAJ 2002; 167:1269–70.
38. Vaxevanis A, Vidalis A. Delirium and atypical antipsychotics: a clinical perspective. Second World Congress on Quality in Clinical Practice; Chalkidiki, Greece; June 3-5, 2004.
39. Schwartz TL, Masand PS. The role of atypical antipsychotics in the treatment of delirium. Psychosomatics 2002; 43:171–174

Corresponding author:
A. Vaxevanis
Hippocratio General Hospital,
Konstantinoupoleos 49, T.K. 54642
Thessaloniki, GREECE