Long-Acting Injectable Risperidone and Hospital Readmission: A Mirror-Image Study Using a National Claim-Based Database in Taiwan

Sir: Poor compliance with antipsychotic medication, which would potentially lead to disease relapse, has been challenging for psychiatrists when treating schizophrenia.[1] Long-acting injection of antipsychotics is an appropriate alternative, since better compliance improves treatment outcomes. Mirror-image studies, in which each patient acts as his/her own control, of long-acting injection of conventional antipsychotics have shown significant decreases in numbers of hospitalizations and days of hospitalization.[2]

The development of atypical antipsychotics has provided a new treatment paradigm based on their superior tolerability, if not efficacy. Risperidone long-acting injection (RLAI) is the first licensed long-acting injectable atypical antipsychotic agent and has recently been reported cost-effective by reducing total admission number and inpatient days in a community-based inpatient setting.[3] To our knowledge, a national claim-based database has never been used in any mirror-image study for RLAI.

Method. The data source used for this 6-month mirror image study was the Psychiatric Inpatients Medical Claims Data (PIMC) from the National Health Research Institute, Taiwan. The PIMC compiled all the health care utilization records during 1996–2006 for patients who had at least 1 psychiatric hospitalization during 1996–2001. The inclusion criteria required that patients (1) could be observed at least 6 months after the first dose of RLAI, (2) had a primary diagnosis of schizophrenia, and (3) were continuously treated with RLAI for at least 6 months. Patients who received at least 75 mg RLAI total for a 3-month time period were considered continuously treated. The differences in number of acute admissions, hospital days, and emergency room visits between the pre- and post-RLAI periods were compared.

Results. A total of 253 from 91,104 patients met the inclusion criteria. As compared to the 6-month pre-RLAI period, the total number of acute admissions was reduced by 35% (136 vs. 88 times, $p = .0007$), and total hospital stays were reduced by 47% (5856 vs. 3080 days, $p = .0002$) in the 6-month post-RLAI period. A reduced number of emergency room visits was also observed (80 vs. 67 times) but was not significantly different ($p = .24$). Since the average hospital stay in acute psychiatric settings was 33 days in Taiwan (data on file; Department of Health, Executive of Yuan, Taiwan; 2007), a secondary analysis to eliminate prolonged hospitalization was conducted by excluding patients who stayed longer than 90 days per admission in the pre-RLAI period. The case number was therefore slightly decreased ($N = 237$), but the differences in acute admissions (115 vs. 80, $p = .0010$) and hospital days (3701 vs. 2160 days, $p = .0026$) remained significant.

The mirror-image study design has 2 major advantages: to assess real-world practice and to have patients act as their own controls[1]; however, the effect of long-acting injectable agents could be overestimated due to the selection bias (e.g., the long-acting injection was started when previous treatment failed) and the exclusion of noncompliant patients. With the claim-based database, we can minimize the latter bias. For future study, a prospective clinical trial or a case-controlled design using the claim data is warranted for generalizability and to provide more information for comparison of utilization across nations.

In conclusion, this 6-month mirror-image analysis showed that RLAI treatment is associated with a reduction of hospital service utilization in Taiwan, and further investigation of long-term outcome is warranted.

The work was supported by grant CMU95-143 from China Medical University (to Dr. Su) and an investigator-initiated grant from Janssen-Cilag Belgium (to Dr. Tang). The authors report no competing interests.

REFERENCES

1. Kane JM, Eerdekens M, Lindenmayer JP, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry 2003;160(6):1125–1132
2. Schooler NR. Relapse and rehospitalization: comparing oral and depot antipsychotics. J Clin Psychiatry 2003;64(suppl 16):14–17
3. Niaz OS, Haddad PM. Thirty-five months experience of risperidone long-acting injection in a UK psychiatric service including a mirror-image analysis of in-patient care. Acta Psychiatr Scand 2007;116(1):36–46

Hui-Chih Chang, M.H.A.
Chao-Hsiun Tang, Ph.D.
School of Health Care Administration
Taipei Medical University
Taipei, Taiwan
Shih-Jen Tsai, M.D.
Taipei Veterans General Hospital and
National Yang-Ming University
Taipei, Taiwan
Feng-Chang Yen, M.D.
Cheng Hsin Rehabilitation Medical Center
Taipei, Taiwan
Kuan-Pin Su, M.D.
Department of Psychiatry and
Mind-Body Interface Research Centre
China Medical University Hospital
Taichung, Taiwan

Aripiprazole-Induced Agitation After Clozapine Discontinuation: A Case Report

Sir: Clozapine continues to be the gold standard for patients with treatment-refractory schizophrenia.[1] However, when patients who have responded to clozapine need to have clozapine treatment discontinued due to a serious adverse event, such as glucose abnormalities, clinicians are often confronted with difficult choices regarding a suitable substitute treatment.

We present a patient who developed acute ketoacidosis while on clozapine treatment and who developed severe agitation and psychotic decompensation with subsequent aripiprazole treatment.

Case report. Ms. A is a 45-year-old undomiciled and unemployed black woman with a history of psychosis and substance abuse with multiple psychiatric hospitalizations who was transferred from a jail facility in September 2006. She was transferred to our state psychiatric center due to her incapacity to assist in her defense related to the charges against her, which was attributed to her psychiatric illness, specifically to auditory

hallucinations and persecutory delusions. This transfer marked the patient's second state psychiatric hospitalization. Prior to her arrest, she was living at a shelter and had been attending a day treatment program for 5 months.

The patient's first hospitalization for psychosis occurred when she was 30 years old. The patient's substance abuse history is significant for cocaine and alcohol abuse since her adolescence. Ms. A has been given DSM-IV diagnoses of schizophrenia, chronic paranoid versus undifferentiated type, and cocaine and alcohol dependence. The patient has a medical history significant for obesity, asthma, and dyslipidemia, but normal glycemic control.

On admission to our hospital, the patient was started on treatment with clozapine while risperidone and haloperidol were discontinued due to nonresponse. Her other medications included valproic acid 500 mg twice daily and nortriptyline 50 mg once daily, along with an albuterol inhaler as needed and ibuprofen as needed for pain control. The patient was titrated upward on clozapine, valproic acid, and nortriptyline. Her psychotic symptoms persisted, however, along with irritability, fluctuating participation on the ward, poor insight, and low frustration tolerance with intermittent verbal abuse toward others. Her glucose levels remained within normal limits. In December 2007, due to a lack of improvement with clozapine, the patient received augmentation with haloperidol 10 mg twice daily as an adjunctive medication. Two months following this addition, the patient developed nonradiating epigastric pain with several episodes of emesis, along with symptoms of dizziness and lethargy. Her blood glucose levels were reported to be in the 400s (mg/dL), and she tested positive for ketones. Ms. A was sent as an emergency to an outside hospital for medical stabilization, where she was deemed to have new-onset diabetes with acute ketoacidosis and spent 1 week at this medical facility, including a stay on the intensive care unit. Clozapine was abruptly discontinued due to concerns about its diabetogenic effects. Aripiprazole 15 mg was substituted for clozapine, while haloperidol 10 mg twice daily was continued.

Upon transfer back to the state psychiatric center after 7 days of clozapine discontinuation, she was noted to be psychiatrically stable with no evidence of delusions or hallucinations, and her mood was documented as euthymic. However, 3 days following her return, the patient was observed to be more restless, pacing the hallways, complaining of insomnia, and exhibiting emotional distress, such as crying inconsolably for help, along with verbally threatening staff members. Levels of orientation and cognitive functions were intact.

After Ms. A had experienced these symptoms for several days, aripiprazole was discontinued, and she was started on molindone treatment, while haloperidol treatment was continued. Molindone was titrated up to 75 mg twice daily, and after 1 week, the patient was noted to be calmer and less demanding on the unit, with limited evidence of psychotic thinking including delusions and hallucinations. She was noted to be more cooperative and alert, needing minimal encouragement for attendance and participation in group activities. Over the course of the next 12 weeks, her clinical state remained stable with the same medication combination.

This case demonstrates a patient who after abrupt discontinuation of clozapine due to acute ketoacidosis received substitute treatment with aripiprazole and developed severe agitation. The agitation eventually responded to the introduction of molindone and discontinuation of aripiprazole. We propose 2 possible etiologies for the post-clozapine decompensation of this patient. First, she may have experienced a withdrawal reaction due to the abrupt discontinuation of clozapine. Although the relationship between clozapine withdrawal and relapse has been closely examined, the mechanism remains elusive and the treatment options ambiguous. Compared to typical antipsychotics, not only is the rate of relapse after discontinuation higher for clozapine, but the observed time course of relapse after discontinuation is more rapid, occurring within 1 to 14 days.[2] Meltzer et al.[3] studied 19 patients with neuroleptic-responsive schizophrenia who received a 2-year clinical trial of clozapine, followed by a clozapine taper with the addition of a typical antipsychotic. The study found that 85% of clozapine withdrawal patients relapsed within 1 week, and Meltzer et al. suggested that a prodrome of nonpsychotic symptoms may occur prior to relapse, with symptoms including insomnia, feeling strange, difficulty concentrating, and agitation. In our patient, some of these nonpsychotic prodromal symptoms were present, but did not appear promptly after clozapine discontinuation. A possible explanation is that the state of acute ketoacidosis masked these symptoms. Nonetheless, these symptoms were not ameliorated by the presence of the typical antipsychotic haloperidol as in Meltzer and colleagues' study.

Several hypotheses have been suggested for the mechanism of clozapine withdrawal psychosis. One hypothesis is that pharmacodynamic adaptations to long-term treatment occur and may act as a stressor when that treatment is discontinued.[4] An example of this adaptation is dopamine receptor supersensitivity. Chouinard and Jones[5] have advanced this hypothesis, defining the syndrome as consisting only of positive symptoms of schizophrenia as a result of relative dopamine hyperactivity in the mesolimbic region. Countering this hypothesis is the significance of the patient's history of cocaine use. Volkow et al.[6] describe how chronic drug consumption results in a marked decrease in dopamine activity. They also go on to discuss how imaging studies have shown lower dopamine D_2 receptor availability in the striatum in cocaine users and how this reduction appears to be long-lasting even after a period of abstinence. Therefore, the patient's history of drug use reduces the likelihood of clozapine withdrawal psychosis as an etiology.

Clozapine is also known to be more weakly bound to receptors, with a shorter duration of receptor occupancy, than other antipsychotics,[7] which could explain the rapid recurrence of symptomatology. Seeman and Tallerico[2] have demonstrated in imaging studies that clozapine is loosely bound to the D_2 receptor, and therefore its rapid release and displacement by dopamine may explain why early clinical relapse occurs upon discontinuation.

Finally, other neurotransmitters may also be at play in the withdrawal state, including acetylcholine and serotonin. Verghese et al.[8] discuss a state of anticholinergic withdrawal, or cholinergic overdrive, as consisting of not only somatic symptoms, but also irritability, anxiety, and sleep disturbance, the latter of which were seen in our patient. On the other hand, Meltzer[9] has suggested that relapse induced by clozapine withdrawal may in part be due to serotonergic receptor alterations in which excessive stimulation of various serotonin receptors may occur during and after clozapine withdrawal.

The second etiologic hypothesis in our case is agitation associated with aripiprazole initiation. It is possible that our patient's symptoms may have been induced by aripiprazole's partial dopamine agonist effect in the context of conversion from long-term blockade of dopamine receptors. Although it has been shown that the rate of relapse with aripiprazole is comparable to those with other second-generation antipsychotics,[10] case reports have shown a temporal relationship between starting aripiprazole and the emergence of psychotic decompensation similar to the one we observed in our patient.[11,12]

The observation of our patient's positive treatment response after discontinuation of aripiprazole and switch to molindone further supports this second etiology. Molindone is a first-generation antipsychotic that has not attained widespread use. It is structurally unique as an indole derivative distinct from other classes of antipsychotics. It has a similar receptor binding profile to quetiapine, with very low binding to all receptors.[13] This profile includes lower affinity for the D_2 receptors compared to haloperidol and chlorpromazine, as well as lower antagonism at the H_1 receptors, which might explain molindone's lower tendency to cause weight gain.[14] Although it is possible that our patient's improvement was due to natural remission, we might speculate that molindone's receptor binding profile was an appropriate fit for our patient, given her prior tolerant response to clozapine, compared to aripiprazole.

Taken together, we feel that this patient's response to the discontinuation of clozapine and subsequent placement on aripiprazole was mainly due to the partial dopamine agonism of aripiprazole. The response abated as soon as aripiprazole was discontinued and when molindone was substituted. Clinicians, when confronted with the choices of alternatives after clozapine discontinuation due to diabetic development, may want to move to an antipsychotic with a low metabolic risk profile such as aripiprazole. However, our case demonstrates that a switch to aripiprazole may not be an appropriate conversion strategy after long-term blockade of dopamine receptors with clozapine.

Dr. Lindenmayer is a consultant for Janssen and Eli Lilly and has received grant/research support from Janssen, Eli Lilly, Pfizer, Organon, Azur, Otsuka, Sumitomo, and AstraZeneca. Dr. Cho reports no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Hippius H. A historical perspective of clozapine. J Clin Psychiatry 1999;60(suppl 12):22–23
2. Seeman P, Tallerico M. Rapid release of antipsychotic drugs from dopamine D2 receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. Am J Psychiatry 1999;156:876–884
3. Meltzer HY, Myung AL, Ranjan R, et al. Relapse following clozapine withdrawal: effect of neuroleptic drugs and cyproheptadine. Psychopharmacology 1996;124:176–187
4. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. Acta Psychiatr Scand 2006; 114:3–13
5. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry 1980; 137:16–21
6. Volkow ND, Fowler JS, Wang G. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology 2004;47:3–13
7. Shiovitz TM, Welke TL, Tigel PD, et al. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. Schizophr Bull 1996;22:591–595
8. Verghese C, Deleon J, Nair C, et al. Clozapine withdrawal effects and receptor profiles of typical and atypical neuroleptics. Biol Psychiatry 1996;39:135–138
9. Meltzer HY. Clozapine withdrawal: serotonergic or dopaminergic mechanism? Arch Gen Psychiatry 1997;54(8):760–763
10. Moeller KE, Shireman TI, Liskow BI. Relapse rates in patients with schizophrenia receiving aripiprazole in comparison with other atypical antipsychotics. J Clin Psychiatry 2006;67(12):1942–1947
11. DeQuardo JR. Worsened agitation with aripiprazole: adverse effect of dopamine partial agonism? J Clin Psychiatry 2004;65(1): 132–133
12. Lea JW, Stoner SC, LaFollette J. Agitation associated with aripiprazole initiation. Pharmacotherapy 2007;27(9):1339–1342
13. Bagnall A, Fenton M, Kleijnen J, et al. Molindone for schizophrenia and severe mental illness. Cochrane Database Syst Review 2007;(1):CD002083
14. Owen R, Cole J. Molindone hydrochloride: a review of laboratory and clinical findings. J Clin Psychopharmacol 1989;9:268–276

Dara Y. Cho, M.D.
Jean-Pierre Lindenmayer, M.D.
Department of Psychiatry
New York University School of Medicine
New York, New York

Overdiagnosis and Underdiagnosis of Bipolar Disorder

Sir: A recent investigation by Zimmerman et al.[1] asserting a problem with overdiagnosis of bipolar disorder compares self-report of previous bipolar diagnoses in 700 patients with diagnoses made with the Structured Clinical Interview for DSM-IV (SCID). They conclude that problems with both underdiagnosis and overdiagnosis of bipolar disorder exist and suggest that the latter may be greater than the former.

In the literature review for their article, the authors fail to cite and discuss one important previous investigation that bears on the question at hand. Hirschfeld et al.[2] screened 649 family practice outpatients with the Mood Disorder Questionnaire (MDQ) to estimate the prevalence of bipolar disorder in a sample population already taking antidepressants for the treatment of depression. Of the sample, 16.2% (105 of 649) reported a prior diagnosis of bipolar disorder. The SCID interview was conducted with 180 of the entire sample. Twenty-nine (16.1%) had a diagnosis of bipolar disorder confirmed, 31 (17.2%) had a new diagnosis of bipolar disorder made, and 14 (7.8%) had a previous diagnosis of bipolar disorder that was not confirmed. Using the distribution of MDQ scores and the results of the completed SCID interviews, the estimated prevalence of bipolar disorder in this family practice sample was 27.9%, most with no prior bipolar diagnosis.

Clearly, accurate diagnosis of bipolar disorder remains a concern. Zimmerman et al.[1] do a thorough job of explaining issues that may contribute to the diagnostic controversy. We suggest that, apart from these and other valid questions about SCID diagnoses compared to diagnoses made by experienced clinicians informed by multiple sources of information and longitudinal follow-up, it may be that clinical setting is also an important factor in the underdiagnosis versus overdiagnosis question. We hope clinicians will maintain awareness that both issues may be operative in clinical practice.

The authors report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Zimmerman M, Ruggero CJ, Chelminski IC, et al. Is bipolar disorder overdiagnosed? J Clin Psychiatry 2008;69(6):935–940
2. Hirschfeld RM, Cass AR, Holt DC, et al. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. J Am Board Fam Pract 2005;18(4):233–239

J. Sloan Manning, M.D.
Michelle E. Kane, Psy.D.
Mood Disorders Clinic
Moses Cone Family Practice Residency
University of North Carolina School of Medicine
Greensboro, North Carolina

Drs. Ruggero and Zimmerman Reply

Sir: We wish to thank Drs. Manning and Kane for bringing to our attention the study by Hirschfeld et al.[1] Their observation is important: clinical setting will affect the relative rate at which bipolar disorder is overdiagnosed or underdiagnosed. The study by Hirschfeld et al., however, raises another variable in this debate that is seldom discussed but perhaps as important, namely, the extent to which researchers, in publishing their results, highlight one set of findings versus another.

Hirschfeld and colleagues' report is a case in point: in their study of bipolar disorder within a family practice setting, they found that, of the 137 patients who had never before been diagnosed with bipolar disorder and who were interviewed, 30 of the patients (21.9%) were newly diagnosed with bipolar disorder with the Structured Clinical Interview for DSM-IV (SCID) and had been improperly treated with antidepressants. Hirschfeld et al. used these data and an imputation technique to estimate prevalence rates, concluding, "A significant number of patients being treated with antidepressants in a primary care setting are likely to have bipolar disorder." Such a finding is important and alarming, and it needs to be brought to the attention of clinicians.

Yet, this conclusion does not tell the whole story. A close look at their results reveals that, of the 43 people who were interviewed and who had a previous bipolar diagnosis, 14 of them (32.6%) were not given a bipolar diagnosis with the SCID. Assuming for the moment that the SCID diagnoses were valid, this finding suggests that, in their sample, not only was bipolar disorder being underrecognized, it was also being overdiagnosed. Nearly a third of the interviewed patients were carrying a bipolar diagnosis that was not confirmed by the SCID. Despite this high rate, the latter phenomenon was not discussed apart from a brief mention in the results. In contrast, the former finding was discussed at length. Such a selective focus creates a one-sided impression: it alerts clinicians to the problem of underdiagnosis but never raises the possibility that the disorder is being overdiagnosed as well.

More broadly, a contentious debate is unfolding over the prevalence of bipolar spectrum disorders, a debate fueled largely by differences in how the disorder is defined. This debate spills over into clinical settings in the form of reports warning that the disorder is woefully underrecognized (e.g., Akiskal and Benazzi[2]). While we do not doubt that bipolar disorder too often goes undetected, we worry that these warnings are selective.

The authors report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Hirschfeld RM, Cass AR, Holt DC, et al. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. J Am Board Fam Pract 2005;18(4):233–239
2. Akiskal HS, Benazzi E. Optimizing the detection of bipolar II disorder in outpatient private practice: toward a systematization of clinical diagnostic wisdom. J Clin Psychiatry 2005;66(7):914–921

Camilo J. Ruggero, Ph.D.
Mark Zimmerman, M.D.
Department of Psychiatry and Human Behavior
Brown Medical School
Providence, Rhode Island