indicate that risperidone may aid in the treatment of depression by augmenting the activity of selective serotonin reuptake inhibitors, including paroxetine.[9] Risperidone and paroxetine interaction can lead to weight gain,[10] priapism,[11] and rarely to serotonin syndrome.[12]

Paroxetine is a substrate and inhibitor of CYP2D6. Metabolism by the CYP2D6 enzyme is saturable at usual doses of paroxetine in 90% of patients.[13] Paroxetine is known to raise the plasma concentration of risperidone and 9-OH risperidone. When paroxetine was added to risperidone therapy, Spina et al[14] observed a 45% increase in mean risperidone plus 9-OH risperidone (risperidone active moiety) concentrations in 10 CYP2D6 extensive metabolizers. Our patient was also receiving galantamine, a competitive inhibitor of acetylcholinesterase. Galantamine is metabolized via CYP2D6 and CYP3A4 but it does not inhibit those enzymes.[15,16] Coadministration of galantamine and risperidone does not increase the serum concentration of risperidone active moiety.[17] Paroxetine can raise galantamine levels by inhibiting CYP2D6 leading to a 40% increase in its bioavailability.[16,18] Galantamine has been reported to cause hypothermia in animal models,[19] but there are no reported cases of galantamine-induced hypothermia in humans in the English literature. In organophosphate poisoning, which usually leads to irreversible inhibition of acetylcholinesterase, humans usually have a hyperthermic response compared with the hypothermic response noted in rodents.[20] Galantamine potentially may have contributed to this patient's hypothermia because of the pharmacokinetic interaction of galantamine and paroxetine or to a possible pharmacodynamic interaction between galantamine and risperidone. However, accumulated clinical data in humans do not support this hypothesis. The decrease in oral intake might be a result of hypothermia and not the cause of it, especially since the patient had no clinical signs of dehydration.

To our knowledge, this is the sixth reported case of risperidone-induced hypothermia. The drug interaction between paroxetine and risperidone may also have been a factor in the development of hypothermia in this patient. Clinicians should take note of this interaction between these 2 agents that are commonly used in the elderly population.

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Impact of Orally Disintegrating Olanzapine on Use of Intramuscular Antipsychotics, Seclusion, and Restraint in an Acute Inpatient Psychiatric Setting

To the Editors:

Intramuscular (IM) conventional antipsychotics have long been used to manage agitation and aggression in the psychiatric inpatient setting.[1] Although generally effective, these preparations

have multiple drawbacks, both in terms of side effects[2–6] and as a consequence of their route of administration. In addition to these factors, treatment invoking the principle of the ''least restrictive environment or intervention'' has become generally accepted in the psychiatric community.[7] This ethical standpoint serves as a compromise between individual rights and severely mentally ill patients' need for treatment, particularly in cases in which impaired reality testing or impulse control may be associated with potentially dangerous behavior. From this perspective, it is important to reduce the use of both invasive routes of medication administration and seclusion and restraint. Finally, a reduction in the number of violent outbursts and episodes of seclusion and restraint may improve patient and staff morale.[8,9]

Recently, literature has emerged showing that, in patients willing to take them, oral atypical antipsychotics are as effective as IM conventional antipsychotics in treating acute psychotic agitation.[10] We report on the use of a rapidly dissolving oral formulation of an atypical antipsychotic (olanzapine; Zyprexa, Eli Lilly and Co, Indianapolis, IN; Zydis, Cardinal Health Pharmaceutical Technologies and Services, Somerset, NJ) on a high-intensity acute inpatient ward.

In November 2002, the psychiatric intensive care unit (PICU) at the West Los Angeles Veterans' Affairs Medical Center (VAMC) replaced 5 mg oral haloperidol with 10 mg olanzapine Zydis (an oral, rapidly disintegrating ''wafer'' formulation) as the ''as needed'' oral antipsychotic of choice for agitation. We hypothesized that the availability of oral olanzapine Zydis would reduce the use of IM antipsychotics in this setting. We also examined the impact of olanzapine Zydis on the use of seclusion and restraint.

In a retrospective chart review, we collected data on the use of p.r.n. IM antipsychotics, seclusion, and restraint for all patients admitted to the PICU at the VAMC in West Los Angeles in the 6 months before the introduction of olanzapine Zydis to the ward formulary (the ''PRE'' group) and in the 6 months after its introduction (the ''POST'' group). The PICU is a locked, 12-bed psychiatric ''crisis'' unit for the most acutely ill psychiatric patients treated at the West Los Angeles VA. The study protocol was approved by the West Los Angeles VAMC Institutional Review Board. An exemption to the requirement for informed consent was obtained by excluding identifying data and by other security measures to protect confidential patient information.

Patient Demographics and Diagnoses

The demographic and diagnostic information for the 2 groups are presented in Table 1. For purposes of analysis, diagnoses assigned at the time of discharge or transfer were divided into 6 categories: (1) primary psychotic disorders (ie, schizophrenia and schizoaffective disorder), (2) substance-induced psychotic disorder and psychotic disorder not otherwise specified, (3) type I bipolar disorder, (4) dementia or delirium, (5) substance use disorders (excluding substance-induced psychotic disorder), and (6) all other diagnoses.[11]

Administration of Intramuscular and Oral Antipsychotics for Acute Agitation

The data regarding the number of administrations of emergent IM conventional antipsychotics for both study groups and of olanzapine Zydis in the POST group are shown in Table 1. There were no significant differences between the 2 groups.

Seclusion and Restraint

In the PRE group, 16 patients (8.8%) were placed in seclusion, and 13 (7.2%) were placed in restraints. In the POST group, 16 patients (9.4%) were placed in seclusion, and 12 (7.0%) were placed in restraints. There were no significant differences between the 2 groups.

DISCUSSION

The results of this study do not support our hypothesis that the availability of

TABLE 1. Patient Demographics, Diagnoses, and Use of p.r.n. Antipsychotics

	PRE Group (n = 181)	POST Group (n = 171)
Age, mean ± SD, y	46.6 ± 8.5	47.5 ± 9.2
Male, n (%)	166 (92)	161 (94)
Length of stay, mean ± SD, d	7.4 ± 8.7	8.2 ± 10.2
Caucasian, n (%)	78 (43)	69 (40)
African American, n (%)	75 (41)	87 (51)
Hispanic, n (%)	20 (11)	13 (8)
Other, n (%)	8 (4)	2 (1)
Primary psychotic disorder, n (%)	44 (24.3)	46 (26.9)
Substance-induced psychosis/psychosis not otherwise specified, n (%)	19 (10.5)	15 (8.8)
Bipolar disorder, n (%)	22 (12.2)	15 (8.8)
Dementia/delirium, n (%)	7 (3.9)	7 (4.1)
Substance use disorder, n (%)	62 (34.3)	66 (38.6)
All emergent IM conventional antipsychotics, n (%)	27 (14.9)	26 (15.2)
''First-line'' emergent IM conventional antipsychotics, n (%)	N/A	20 (11.7)
''Second-line'' emergent IM conventional antipsychotics, n (%)	N/A	9 (5.3)
Emergent oral olanzapine Zydis, n (%)	N/A	37 (21.6)

PRE indicates patients admitted in 6-month period before addition of olanzapine Zydis to the ward formulary; POST, patients admitted in six-month period after addition of olanzapine Zydis to the ward formulary; N/A, not applicable; first-line, before administration of olanzapine Zydis; second-line, after administration of olanzapine Zydis (for a given episode of agitation).

a rapidly disintegrating formulation of an atypical antipsychotic for emergent use would reduce the use of IM antipsychotics or of seclusion or restraint in an acute inpatient psychiatric setting. In comparison with a similar patient population admitted before the addition of olanzapine Zydis to the ward formulary, the study group demonstrated no change in use of IM antipsychotics, seclusion, or restraint. While this may suggest that the introduction of olanzapine Zydis to the ward formulary did not reduce the use of more restrictive interventions, the lack of a quantitative measurement of illness severity (eg, a Global Assessment of Functioning score at the time of admission) precludes drawing any firm conclusions regarding the impact or lack of impact of the availability of p.r.n. olanzapine Zydis on these outcome measures. In other words, it is possible that a difference in overall illness severity between the 2 groups may have obscured any potential benefits such as reduced use of IM antipsychotics, seclusion, or restraint. However, this possible explanation seems less likely when considering the lack of any known changes in the VA population accessing services during the 12 months of the study and the similar demographics and distribution of diagnoses in the 2 groups.

This study has several limitations. Patients must agree, if only by assent, to take any oral medication. Patients who are extremely ill or acutely agitated may refuse oral medications, precluding this treatment option and necessitating IM medication when agitation requires emergent medication. We did not assess the role of patient refusal in the selection of interventions for emergent agitation. Similarly, we did not address the role of nursing staff's clinical judgment regarding these interventions.

Another limitation of the study is its naturalistic design. We did not address variables such as standing antipsychotic or mood-stabilizing medication orders or the use of p.r.n. oral benzodiazepines. In fact, in the acute inpatient setting studied here, oral benzodiazepines, primarily lorazepam, are used frequently on a p.r.n. basis for anxiety and agitation. It is possible that those who did not respond to benzodiazepines had a more severe level of agitation more likely to require IM medication. Thus, there may have been a tradeoff between use of benzodiazepines and olanzapine Zydis after the introduction of the latter. A study in which only antipsychotics were used might provide a more definitive comparison of the utility of oral atypical antipsychotics versus IM medications in controlling severe agitation.

It should also be remembered that although olanzapine Zydis dissolves rapidly in the mouth, its absorption occurs via the gastric mucosa. Therefore, its onset of action is equivalent to the tablet form.[12] This relatively slow onset of action (peak plasma level at 6 hours after administration) may in part explain the lack of effect seen for olanzapine Zydis in reducing emergent IM use and seclusion and restraint in the present study. It is possible that IM antipsychotics, seclusion, or restraint was used before the onset of the clinical effect of olanzapine Zydis.

The use of IM atypical antipsychotics, such as olanzapine and ziprasidone, both of which have been recently approved for acute use in the United States, would avoid this pharmacokinetic disadvantage of oral olanzapine while maintaining atypical antipsychotic efficacy. These agents greatly reduce the frequency of many of the adverse reactions seen with conventional antipsychotics, but obviously not those consequent to the IM route of administration. Nevertheless, these agents may address the acute treatment needs of patients too agitated to benefit from an oral agent.

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Altered Expression of Myeloperoxidase Precursor, Myeloid Cell Nuclear Differentiation Antigen, Fms-related Tyrosine Kinase 3 Ligand, and Antigen