Olanzapine for Self-Injurious, Aggressive, and Disruptive Behaviors in Intellectually Disabled Adults: A Retrospective, Open-Label, Naturalistic Trial

David S. Janowsky, M.D.; L. Jarrett Barnhill, M.D.; and John M. Davis, M.D.

Background: The effectiveness of olanzapine in treating challenging behaviors in the intellectually disabled and its ability to substitute for conventional antipsychotic drugs were evaluated.

Method: A total of 20 institutionalized adults with a mean age of 42.7 years (range, 18–55 years) with intellectual disability and aggression, self-injurious behavior, destructive/disruptive behavior, or combinations of these behaviors were studied. These individuals were receiving multiple psychotropic medications at baseline and were given additional treatment with the atypical antipsychotic agent olanzapine. The mean dose of olanzapine was 9.1 mg/day (range, 2.5–22.5 mg/day). Effectiveness was determined by retrospective review of the summaries of quarterly neuropsychiatric behavioral reviews and retrospective review of longitudinal behavioral graphs of target symptoms. Data were collected from 1995 to 2000.

Results: A significant decrease in global challenging behaviors and specific target behaviors (i.e., aggression, self-injurious behaviors, destructive/disruptive behaviors) occurred ($p < .05$). A numerical decrease in the dosage of concurrent conventional antipsychotic medications occurred over the course of the first 6 months of olanzapine therapy, and a statistically significant ($p < .005$) decrease from the start of olanzapine therapy occurred in those subjects who received olanzapine for longer than 6 months (mean = 20.3 months). A significant increase in weight occurred in the subject group during the first 6 months of olanzapine treatment ($p < .006$), and sedation and constipation were the other common side effects noted.

Conclusions: Olanzapine was found to be effective in the treatment of challenging behaviors in the intellectually disabled and in part could be substituted for administration of conventional antipsychotic drugs.

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Corresponding author and reprints: David S. Janowsky, M.D., Dept. of Psychiatry, CB# 7175, University of North Carolina, Chapel Hill, NC 27599-7175 (e-mail: David_Janowsky@med.unc.edu).

Intellectual disability and developmental disabilities are frequently associated with dangerous and costly aggression toward self (self-injurious behavior including biting, self-hitting, head banging, etc.), aggression toward others (hitting, biting, kicking, etc.), and destructive/disruptive behaviors (breaking or overturning furniture, breaking windows, screaming, running, etc.).[1–3] These challenging behaviors occur with increasing frequency as IQ decreases. The most widely used medications for the treatment of the challenging behaviors described above are the antipsychotic drugs. Previously, those used consisted of the older typical conventional antipsychotic drugs.[1,4] More recently, the newer "atypical" antipsychotic drugs, such as clozapine,[5] risperidone,[6–14] quetiapine,[15] and olanzapine,[16–20] with their common biochemical property of an increased ratio of serotonin ($5\text{-}HT_2$) to dopamine (D_2), have been utilized to treat challenging behaviors in individuals with intellectual disability.[4]

The current study evaluated the effectiveness of olanzapine in treating aggression, self-injurious behavior, and disruptive behaviors in intellectually disabled, institutionalized adults. A secondary goal was to determine if olanzapine was as effective as, and/or could be partially or completely substituted for, conventional antipsychotic drugs.

The literature describing olanzapine utilization in intellectually disabled individuals is limited. Horrigan et al.[16] reported a single case in which olanzapine was effective in treating a 10-year-old autistic boy for aggression and repetitive behaviors. Potenza et al.[17] reported an open-label study in which olanzapine was administered to 8 individuals (4 children/adolescents and 4 adults) with autism and/or pervasive developmental disorder. After 12 weeks, 6 of the 8 were considered responders. These individuals had significant improvements in autism, motor restlessness, hyperactivity, social relatedness, affective reactions, self-injurious behavior, aggression, irritability or anger, anxiety, and depression. More recently, McDonough et al.[18] reported that olanzapine reduced the stereotypic form of chronic self-injurious behavior in 4 of 7 individuals with various levels of learning disability. Williams et al.[19] treated 12 adults with mild or moderate intellectual disability who had a variety of reasons for being given olanzapine, including psychosis, challenging behaviors, side effects of other drugs, and inadequate treatment responses.

Table 1. Descriptive Information on 20 Institutionalized Intellectually Disabled Adults Receiving Olanzapine for Challenging Behaviors

Patient	Gender/Age (y)/ Ethnicity	Psychiatric Diagnosis	Level of Retardation	
			Cognitive	Adaptive
A	M/45/AA	Behavioral disorder, explosive personality disorder	Severe	Severe
B	M/52/W	Behavioral disorder NOS	Profound	Profound
C	M/53/W	Mood disorder NOS, chronic schizophrenia	Severe	Severe
D	M/18/W	Autism	Severe	Profound
E	F/40/AA	Bipolar disorder	Severe	Profound
F	F/33/W	Bipolar disorder, intermittent explosive disorder	Severe	Severe
G	M/52/W	No diagnosis	Profound	Profound
H	F/54/W	Psychosis NOS	Moderate	Profound
I	M/54/W	Paranoid schizophrenia, OCD	Mild	Profound
J	M/30/W	Autism, bipolar disorder	Profound	Profound
K	M/24/W	Behavioral disorder NOS, intermittent explosive disorder	Profound	Profound
L	F/41/W	Bipolar disorder, behavioral disorder NOS	Moderate	Profound
M	F/55/AA	Schizophrenia or bipolar disorder	Profound	Profound
N	F/38/AA	Major depressive disorder with psychosis	Severe	Profound
O	F/49/AA	Intermittent explosive disorder	Mild	Severe
P	F/50/AA	Bipolar disorder	Severe	Profound
Q	F/40/W	Bipolar disorder	Profound	Profound
R	F/43/W	Behavioral disorder NOS, bipolar disorder	Profound	Profound
S	F/46/W	Autism, schizophrenia, OCD	Profound	Moderate
T	M/36/W	Bipolar disorder	Moderate	Profound

Abbreviations: AA = African American, F = female, M = male, NOS = not otherwise specified, OCD = obsessive-compulsive disorder, W = white.

These authors found that 58.3% of their subjects "greatly improved," a percentage essentially the same as for those who improved on risperidone treatment. Finally, Kemner et al.[20] studied 25 children aged 6 to 16 years with either autistic or pervasive developmental disorder who received olanzapine. Statistically significant improvement in irritability, hyperactivity, and excessive speech and in Clinical Global Impressions-Severity of Illness scores, target symptom scores, socially inadequate behavior, and several aspects of communication occurred. However, the authors concluded that the clinical relevance of olanzapine may be limited, since the effects on the Clinical Global Impressions-Improvement scale were small and because only 3 children were considered responders on the latter scale.

Use of the atypical antipsychotic agents, including olanzapine, is appealing because, in studies of adult schizophrenia, parkinsonian symptoms, dystonias, withdrawal dyskinesias, and tardive dyskinesia occur less frequently than with conventional antipsychotic drugs.[21–24] Atypical antipsychotic agents also may be more effective than conventional antipsychotics in treating the negative symptoms of schizophrenia.[24] Their increased efficacy, compared with conventional antipsychotics, in helping treatment-resistant schizophrenic patients is controversial, with negative[25] and positive[26] reports existing. Atypical antipsychotic agents may have fewer deleterious cognitive effects than conventional antipsychotic drugs, and, indeed, there is some evidence that they may actually improve cognition.[27,28]

For the most part, studies utilizing atypical antipsychotic medications to treat challenging behaviors in intellectually disabled individuals have reported positive outcomes.[1,4] However, as with studies of conventional antipsychotic drugs,[4] treatment of the intellectually disabled with atypical antipsychotic drugs is relatively ineffective in some reports,[4,15,20] and the vast majority of trials have been case series that enrolled small numbers of subjects.[4,5]

METHOD

Subjects

Subjects in the study were 20 adults with intellectual disability who received olanzapine for the treatment of aggression, self-injurious behaviors, destructive/disruptive behaviors, or combinations of such behaviors. All participants were individuals institutionalized at a large state facility for the treatment of the intellectually disabled, the Murdoch Center in Butner, N.C. Profiles of the individuals utilized in the study are shown in Table 1. The majority of the individuals had either severe or profound cognitive and adaptive intellectual disability. The study group consisted of 9 men and 11 women. Their mean ± SD age was 42.7 ± 10.5 years, with an age range of 18 to 55 years. Fourteen were white, and 6 were African American. Over the years, they had previously been assigned a variety of psychiatric diagnoses by consulting psychiatrists and/or other mental health professionals. These included autism, behavioral disorder not otherwise specified (NOS), bipolar disorder, affective disorder, mood disorder NOS, obsessive-compulsive disorder, schizophrenia, paranoia, psychosis NOS, and explosive personality disorder. In general, psychiatric diag-

Table 2. Conventional and Atypical Antipsychotic Drug Doses Given 6 Months Before, Immediately Before, and 6 Months After Institution of Olanzapine Therapy in 20 Intellectually Disabled Adults[a]

Patient	Olanzapine Dose (mg/d)	Concurrent Antipsychotic Medication	Conventional Antipsychotic Drug Dose (chlorpromazine equivalents)			
			6 Mo Before	Immediately Before	6 Mo After	End of Study
A	7.5	Thioridazine	300	300	300	175
B	10.0	Thioridazine	100	95	95	75
C	10.0	Loxapine	540	540	90	0
D	22.5	None	…	…	…	…
E	5.0	Haloperidol	450	300	175	NA
F	20.0	None	…	…	…	…
G	5.0	Thiothixene	125	125	25	0
H	5.0	Haloperidol	800	650	300	NA
I	7.5	Haloperidol	200	200	0	0
J	15.0	Haloperidol	850	350	850	NA
K	15.0	Thioridazine	190	190	190	NA
L	7.5	Thioridazine	50	50	25	9
M	7.5	Thiothixene	225	250	0	0
N	2.5	Thiothixene	425	325	425	325
O	5.0	Haloperidol	1750	1750	1500	1000
P	10.0	Haloperidol	600	600	600	NA
Q	7.5	Quetiapine	50	300	0	NA
R	5.0	Haloperidol	1000	900	925	NA
S	10.0	Haloperidol	200	200	150	104
T	5.0	Thioridazine	100	100	100	90

[a]The mean ± SD olanzapine dose was 9.1 ± 5.3 mg/day. Mean ± SD conventional antipsychotic doses in chlorpromazine equivalents were as follows: 6 months before, 445 ± 431; immediately before, 370 ± 353; 6 months after, 292 ± 395; end of study, 152 ± 284.
Abbreviation: NA = not applicable; no data for timepoint. Symbol: … = no antipsychotic drug given.

noses had been clinically derived over the years utilizing DSM-III-R and DSM-IV criteria.

The individuals in the study were placed on olanzapine treatment because of an inadequate response to other psychopharmacologic agents (usually after a trial of conventional antipsychotic drugs), the development of unacceptable side effects from conventional antipsychotic drugs, or the desire to switch to a drug that had less potential for causing extrapyramidal symptoms and/or tardive dyskinesia. As shown in Table 2, of those studied, 17 of the 20 subjects were receiving conventional antipsychotic drugs and 1 was receiving quetiapine at the time that olanzapine was started. As shown in Table 3, 18 of 20 individuals studied were receiving 1 or more non-neuroleptic psychotropic medication and/or anticonvulsant medication at baseline. Those previously placed in behavioral intervention programs had these programs continued throughout the study. Permission to treat each individual with olanzapine was obtained from the individuals' respective guardians. The study was approved by the institutional review boards of the University of North Carolina at Chapel Hill and the Murdoch Center.

Evaluation

The study evaluated all individuals at the Murdoch Center with intellectual disability in whom olanzapine had been or was being administered between the years 1995 and 2000. The study specifically consisted of abstracting the results of neuropsychiatric behavioral review (NBR) conference reports that had been generated quarterly or more frequently in individuals requiring medications for behavioral control.

The NBR conferences consisted of mandated, regular quarterly meetings of a subject's treatment team, usually consisting of a cottage manager, psychologist, nurses, nursing assistant(s), primary care physician, pharmacist, educator, and consulting psychiatrist. The team reviewed the progress and evaluated responses to medications of all individuals receiving medications for behavioral purposes. During each conference, a written summary reviewing the subject's course and changes since the last NBR was presented. The summary consisted of (1) the subject's diagnosis, (2) psychotropic and other medications given and changes in medications made since the last review, (3) significant adverse or side effects noted, (4) significant laboratory tests and serum drug levels noted (data including fasting glucose levels obtained approximately every 6 months), (5) weight changes (data obtained monthly), (6) details of changes in target symptoms, (7) any changes in behavioral intervention plans, (8) monitoring methods, and (9) progress toward goals. The summary was presented by the nursing and other unit staff. Nurses noted on the summary those side effects and unusual laboratory values observed since the last review as abstracted from the subjects' medical records. In addition, a longitudinal quantitative graphing of each individual's target behaviors was provided by the unit psychologist. The conferences had a special focus on making decisions concerning the utilization of medications given for the purpose of minimizing severe target

Table 3. Non-Antipsychotic Psychotropic Medications Given 6 Months Before, Immediately Before, and 6 Months After Addition of Olanzapine in 20 Intellectually Disabled Adults[a]

Patient	Medications 6 Mo Before Olanzapine	Concurrent Medications At Olanzapine Start	Concurrent Medications After 6 Mo of Olanzapine
A	Carbamazepine, lithium	Carbamazepine, lithium	Carbamazepine, lithium
B	Carbamazepine	Carbamazepine	Carbamazepine
C	Carbamazepine	Carbamazepine	Carbamazepine
D	Fluvoxamine	Fluvoxamine	Fluvoxamine
E	Lithium, benztropine	Lithium, benztropine	Lithium, benztropine
F	Propranolol, clomipramine, clonazepam, carbamazepine	Propranolol, clomipramine, gabapentin, clonazepam	Propranolol, clomipramine, gabapentin, clonazepam
G	Trihexyphenidyl	Trihexyphenidyl	Trihexyphenidyl
H	Valproic acid, trihexyphenidyl	Valproic acid, trihexyphenidyl	Valproic acid, trihexyphenidyl
I	Lithium	Topiramate	Topiramate
J	Lithium	…	…
K	Gabapentin, paroxetine	Gabapentin	Gabapentin
L	Lithium	Lithium	Lithium
M	Lithium, trihexyphenidyl	Lithium, trihexyphenidyl	Lithium
N	Paroxetine	Paroxetine	Paroxetine
O	Topiramate	Topiramate	Topiramate
P	Topiramate	Carbamazepine	Carbamazepine
Q	Topiramate	Topiramate	Topiramate
R	Carbamazepine, lorazepam	Carbamazepine, lorazepam	Carbamazepine, lorazepam
S	…	…	…
T	Lithium, carbamazepine	Lithium, carbamazepine	Lithium, carbamazepine

[a]Carbamazepine, gabapentin, topiramate, and valproic acid were used for seizure control in all but 3 instances.
Symbol: … = no concurrent medication was given.

behaviors. From each conference, a permanent report was generated by the consulting psychiatrist, or by the patient's physician when the psychiatrist was not present. This report was placed in the record of the individual reviewed. It was these NBR conference reports that were utilized as sources of data for the current study.

As shown in Table 4, the frequency of targeted aggressive, self-injurious, and disruptive behaviors was evaluated by totaling the longitudinal behavioral ratings provided by the unit psychologist. The cumulative number of recorded target behaviors, as graphed by the unit psychologist, was evaluated for the 6 months before and the 6 months after olanzapine was started (or for less time when either period was shorter). Methods of evaluating behavior varied from unit to unit and from subject to subject, but often consisted of nursing reports or interval observations.

In addition, each NBR report was evaluated using a global 7-point rating scale, with 1 equaling no symptoms and 7 equaling severe symptoms. The reviews were evaluated globally for overall general status of the patient, but with special consideration of comments about aggressive, self-injurious, and disruptive behaviors. For purposes of data analysis, as shown in Table 5, evaluation of the global scores of target behaviors occurred 6 months before, just preceding, and 6 months after olanzapine therapy was begun and at the time of the last recorded evaluation after beginning olanzapine therapy, if this occurred at a different time from the evaluation performed 6 months after the beginning of treatment.

In addition, as shown in Table 2, the doses of conventional antipsychotic drugs (e.g., thioridazine, haloperidol), expressed in chlorpromazine equivalents, were determined at 6 months before, just before, 6 months after, and at the end of the study, or when olanzapine was discontinued.

Statistical Analysis

Mean and standard deviation values were generated using STATA Version 5.0. (Stata Corporation, College Station, Tex.). Statistics were computed using 2-tailed paired t tests. Statistical significance was set at an alpha level of .05 or lower.

RESULTS

Following the institution of olanzapine therapy (maximum mean dose = 9.1 ± 5.3 mg/day [mean ± SD]; range, 2.5–22.5 mg/day), a significant decrease in the quantitatively measured target behaviors, as recorded and graphed by unit psychologists, occurred. As shown in Table 4, aggression decreased in 13 of 14 individuals studied, self-injurious behaviors decreased in 6 of 7, and disruptive behavior/other behaviors decreased in 8 of 11 after olanzapine treatment (aggression: $t = 3.02$, $df = 13$, $p < .01$; self-injurious behavior: $t = 2.54$, $df = 6$, $p = < .044$; disruptive and other behaviors: $t = 2.72$, $df = 10$, $p < .021$).

Table 5 shows the individual and mean global ratings of the subjects studied at 6 months before and just before starting olanzapine, 6 months after starting olanzapine, and at the end of the study. Of the 20 individuals studied, 16 showed a decrease in the global ratings from 6 months before and just before olanzapine treatment to 6 months

Table 4. Target Behaviors for the 6 Months Before and 6 Months After the Start of Olanzapine Treatment in 20 Mentally Retarded Adults[a]

	Cumulative No. of Behaviors per 6 Mo					
	Aggression		Self-Injurious Behavior		Disruptive Behavior	
Patient	Before	After	Before	After	Before	After
A	8	3	…	…	2	4
B	13	12	…	…	…	…
C	…	…	…	…	47	9
D	…	…	…	…	95	13
E	130	60	…	…	100	9
F	16	16	14	14	…	…
G	…	…	3	2	…	…
H	…	…	…	…	1	3
I	19	1	…	…	…	…
J	6	3	…	…	36	41
K	8	1	27	4	…	
L	…	…	60	50	…	…
M	8	0[b]	…	…	…	…
N	…	…	…	…	15	10
O	80	18	…	…	20	10
P	15	7	6	4	51	21
Q	130	70	…	…	…	…
R	5	3	15	9	…	…
S	24	0[b]	14	0[b]	65	6
T	17	5	…	…	20	12

[a]The method of observation and the frequency of observations of behaviors varied between individuals studied. Mean ± SD numbers of behaviors were as follows: aggression: before, 34.2 ± 44.7; after, 14.2 ± 22.0; self-injurious behavior: before, 19.8 ± 19.3; after, 11.9 ± 17.4; disruptive behavior: before, 41.1 ± 34.4; after, 12.5 ± 10.6.
[b]Zeroes indicate that no behaviors occurred.
Symbol: … = no data obtained.

Table 5. Global Behavioral Ratings of 20 Adults With Mental Retardation 6 Months Before, Immediately Before, and 6 Months After Beginning Treatment With Olanzapine[a]

	Global Behavioral Rating			
Patient	6 Mo Before	Immediately Before	6 Mo After	Study End
A	2.7	2.3	2.0	2.0
B	2.3	2.3	2.3	3.3
C	2.3	2.3	1.7	2.0
D	3.0	3.7	1.7	1.7
E	3.7	2.7	2.3	NA
F	2.7	3.0	4.0	2.0
G	2.3	2.3	1.7	2.0
H	2.7	3.0	2.3	NA
I	2.3	5.0	2.0	2.7
J	3.7	4.3	2.7	NA
K	4.3	6.0	3.3	NA
L	3.3	3.3	4.0	2.3
M	2.7	3.3	2.3	1.3
N	3.0	5.7	1.7	2.3
O	5.3	5.3	3.0	2.3
P	4.0	5.3	2.3	NA
Q	5.0	6.3	3.3	NA
R	3.7	4.0	3.3	NA
S	1.7	1.7	2.0	2.0
T	3.0	3.3	2.3	1.3

[a]Global behavior was rated on a 1–7 scale (no maladaptive behavior to severe maladaptive behavior) based on the neuropsychiatric behavioral review (NBR) summary reports generated 6 months before, just before, and 6 months after beginning olanzapine treatment and when the last NBR utilizing olanzapine was made (study end). Each NBR evaluated the preceding 3 months. Mean ± SD ratings were as follows: 6 mo before, 3.23 ± 0.91; immediately before, 3.54 ± 1.38; 6 mo after, 2.49 ± 0.70; study end, 2.28 ± 0.72.
Abbreviation: NA = not applicable; no data for timepoint.

following the institution of olanzapine treatment. In addition, 3 subjects showed an increase in global ratings, and 1 showed no change. The mean global rating scale score fell 30% from the NBR just before olanzapine was started to the 6-month post-olanzapine evaluation ($t = 4.01$, $df = 19$, $p < .0008$). A significant decrease also occurred between the evaluations 6 months before and 6 months after the start of olanzapine treatment ($t = 3.54$, $df = 19$, $p < .002$). For the 13 subjects in whom olanzapine treatment continued beyond 6 months (mean = 20.3 months after beginning olanzapine), an overall decrease in ratings occurred between just before the start of olanzapine therapy and the end of the study ($t = 3.43$, $df = 12$, $p < .005$) and between 6 months before the start of olanzapine therapy and the end of the study ($t = 2.53$, $df = 12$, $p < .025$). An increase in ratings occurred between 6 months before and just before olanzapine was started ($t = 2.7$, $df = 19$, $p < .0014$). No significant difference was noted between the ratings 6 months after the start of treatment and those at the end of the study ($t = 1.03$, $df = 12$, $p < .32$).

As shown in Table 3, most of the individuals studied were receiving non-antipsychotic psychotropic drugs and/or antiseizure drugs prior to and after the institution of olanzapine treatment. The most commonly utilized of these medications were carbamazepine, gabapentin, valproic acid, and topiramate (all used to treat seizures except in 3 subjects); the selective serotonin uptake inhibitors; and/or one of the benzodiazepines. The doses of these medications, given before and after institution of olanzapine, remained generally stable throughout the study period.

Table 2 lists the typical (i.e., conventional) and atypical antipsychotic medications given prior to and during the institution of olanzapine therapy. Of the 18 subjects who received these medications, 8 were receiving haloperidol, 5 were receiving thioridazine, 3 were receiving thiothixene, 1 was receiving loxapine, and 1 received a trial of quetiapine at the beginning of olanzapine treatment. Table 2 demonstrates that in 12 of the 18 cases, a decrease in the typical antipsychotic drug dose occurred after olanzapine was begun, and of these, termination of the typical antipsychotic drugs occurred in 5. The average decrease in chlorpromazine equivalents from just prior to the institution of olanzapine until 6 months following the start of olanzapine therapy approached statistical significance ($t = 1.66$, $df = 17$, $p < .11$). The decrease from 6 months before until 6 months after olanzapine therapy was begun was significant ($t = 3.25$, $df = 17$, $p < .005$). Similarly, the decreases in chlorpromazine equivalents from just prior to beginning olanzapine therapy until the

end of the study and from 6 months before therapy until the end of the study were statistically significant ($t = 2.7$, $df = 10$, $p < .021$; $t = 2.9$, $df = 10$, $p < .015$, respectively). A near-significant decrease in chlorpromazine equivalents occurred between 6 months after starting olanzapine treatment and the end of the study ($t = 1.9$, $df = 10$, $p < .080$). The continuation group receiving olanzapine averaged 20.3 months of olanzapine treatment, and the decrease in dose of typical antipsychotic drug in these patients was significant ($p < .005$)

The NBR reports indicated that olanzapine caused several side effects. Sedation was reported in 4 individuals. Constipation occurred in 2 subjects, and a gait problem occurred in 1. A mean weight gain of 7.4 lb (3.4 kg) occurred in the subject group between the NBR occurring just before and the NBR occurring 6 months after olanzapine therapy was started (pre-olanzapine weight = 151.5 lb [68.2 kg], 6 months post-olanzapine administration weight = 158.9 lb [72.0 kg], $t = 3.01$, $df = 19$, $p < .006$). A weight gain of 10 lb (4.5 kg) or more occurred in 5 of the subjects over the above period. None of the laboratory tests mentioned in 18 of the 20 NBR forms indicated that olanzapine induced increases in serum glucose levels.

DISCUSSION

Our results demonstrate that olanzapine therapy, usually given in addition to conventional or typical antipsychotic drug therapy and in addition to other concurrent psychotropic drug therapies, caused a statistically significant decrease in aggressive, self-injurious, and disruptive behaviors. Also, after olanzapine was added to the treatment regimen, the average dosage of conventional antipsychotic drugs was decreased in a number of subjects, with 5 of the subjects actually stopping conventional antipsychotic drugs completely. However, at 6 months after the institution of olanzapine therapy, the decrease in conventional antipsychotic medications only approached statistical significance. For those subjects who were evaluated after receiving more than 6 months of olanzapine therapy, a statistically significant decrease in dosage did occur.

The observation that the addition of olanzapine eventually was associated with a decrease in the dosage of conventional antipsychotic drugs or a cessation of administration may be clinically important. Generally, it is presumed that atypical antipsychotic drugs are less likely to cause tardive dyskinesia than are conventional antipsychotic drugs. Significantly, the incidence of the development of tardive dyskinesia in intellectually disabled populations requiring chronic antipsychotic drugs is relatively high.[1] Thus, if an atypical antipsychotic drug such as olanzapine proves helpful in treating challenging behaviors in the latter population, this may be especially important for the prevention of tardive dyskinesia.

However, pitfalls do exist concerning the use of olanzapine and other atypical antipsychotic drugs. Olanzapine and clozapine especially, as well as quetiapine and risperidone, are known to cause weight gain,[29,30] and all of these cause sedation. Although somewhat controversial with respect to implications, clozapine and olanzapine and, to a lesser extent, quetiapine and risperidone have been reported to cause increases in the incidence of diabetes, serum glucose levels, glucose intolerance, and serum lipids (i.e., hyperlipidemia).[30–33] The above risk factors (i.e., abdominal obesity, increased serum lipids, and glucose intolerance) are 3 of the risk factors found to be highly related to cardiovascular disease in the Framingham Heart Study.[34] Such considerations led Koro et al.[32] to specifically suggest that the metabolic consequences of olanzapine use be given serious consideration by treating physicians and caused Meyer[30] to assert that careful evaluation and relatively frequent monitoring of weight gain, glucose levels, and serum lipid levels (i.e., triglycerides, cholesterol) should occur before and at least over the first year of treatment when using atypical antipsychotic drugs, especially in high-risk subjects. With respect to electrocardiographic changes, Glassman and Bigger[35] have concluded that, in contrast to thioridazine and several other conventional antipsychotic drugs, there is no convincing evidence that ziprasidone, olanzapine, quetiapine, or risperidone significantly cause an increase in sudden death or torsades de pointes. Nevertheless, when adding atypical antipsychotic drugs that cause QT_c increases[35] to conventional antipsychotic drugs such as thioridazine, which also cause increased QT_c intervals, consideration of the potential for an additive increase in QT_c interval would seem prudent. Finally, alternative drugs can be used to treat the behaviors studied herein; these include lithium, carbamazepine, valproic acid, the selective serotonin uptake inhibitors, buspirone, and β-adrenergic blocking agents.[1]

The current study ended in the year 2000, at a time when the effects of olanzapine and other atypical antipsychotic drugs on metabolic parameters were less well known and serum lipid levels were not routinely monitored. Nevertheless, fasting serum glucose levels in the current evaluation were routinely obtained, and none of the 18 subjects in whom they were obtained were noted to have elevated glucose levels. However, the limitation of these data is that they are only reflective of those NBR information sheets provided by the nursing staff that reported "significant results," and thus aberrant data may have gone unnoted. Furthermore, laboratory tests were obtained at different times after beginning olanzapine therapy in different subjects. Thus, although most of our subjects had laboratory values drawn while receiving olanzapine, we do not believe our results accurately reflect whether glucose changes actually occurred.

Our subject group showed an overall mean statistically significant weight gain of 7.4 lb (3.4 kg), and 5 subjects

showed a 10-lb (4.5-kg) or greater weight gain during the first 6 months that olanzapine was administered. Weight gain was managed by dietary control and/or eventually switching to another atypical or conventional antipsychotic agent.

Our study has a number of other limitations and several unique positive aspects. The work was a retrospective analysis of data in which the effects of adding olanzapine to a conventional antipsychotic drug and/or other psychotropic drugs were studied naturalistically. As described above, notation of side effects and significant aberrant laboratory values was summarized by the report that the nurses submitted at the time of the NBR and could have omitted some important observations. Also, evaluation of side effects in a group of individuals with severe intellectual disability is challenging at best. Although our global ratings are numerical, the study is probably best considered as a qualitative or case study evaluation of olanzapine's effects.

Our study did not include placebo controls, and no blinding occurred. Conversely, our cases were not subjected to a washout period such as occurs in most controlled studies. A washout strategy has the potential of causing an increase in baseline symptoms due to withdrawal effects or the unmasking of symptoms. Also, although multiple drugs were used in the treatment of our subject group, thus making difficult the ascertainment of "pure" effects, this situation does approximate the usual clinical situation.

Diagnostically, our study group was diverse, and in a group of individuals with severe and profound intellectual disabilities, psychiatric diagnosis is at best difficult to make. The diagnoses were made clinically, generally based on DSM-III-R or DSM-IV criteria, rather than utilizing a formal diagnostic protocol design for research purposes. Nevertheless, there was no evidence from our study that any one diagnostic group was differentially affected by olanzapine treatment.

Other limitations of our study include the relatively small sample size and a clinically determined dosing schedule. Also, the longitudinal evaluations of specific target behaviors varied from subject to subject and from residential unit to unit with respect to the type of behaviors studied, the timing of the observations made, and the frequency, length, and intensity of the observations made.

Given our study design, it is possible to argue that the individuals studied required no antipsychotic medication at all and that it was the lowering of the conventional antipsychotic medication dosages that led to the overall improvement. However, it is noteworthy that in many of our subjects, previous attempts to lower and/or stop antipsychotic medication dosages had yielded a significant intensification of target symptoms. Furthermore, since our subjects were in most cases receiving other psychotropic medications before and after the institution of olanzapine, it is possible that the improvements noted were based on drug-drug interactions, rather than on the pure effects of olanzapine alone.

In spite of the above considerations, our results suggest that the addition of olanzapine to an existing conventional antipsychotic drug significantly improves aggressive, self-injurious, and destructive/disruptive behaviors. In many, but not all, cases, conventional antipsychotic drug dosages could be lowered below the lowest doses that had been effective previously and/or could be stopped. What is not clear is whether a higher dose of a conventional antipsychotic drug would in itself have caused a significant decrease in challenging behaviors equal to the effects of olanzapine. Nevertheless, our results support a limited literature suggesting that olanzapine specifically, and atypical antipsychotic drugs more generally, are useful in the treatment of challenging behaviors.

Drug names: benztropine (Cogentin and others), buspirone (BuSpar and others), carbamazepine (Tegretol, Epitol, and others), chlorpromazine (Thorazine, Sonazine, and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), gabapentin (Neurontin), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), olanzapine (Zyprexa), paroxetine (Paxil), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), topiramate (Topamax), valproic acid (Depakene and others), ziprasidone (Geodon).

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