The Effects of Molindone as a Concomitant Medication on Aggressive Behavior

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Abstract

Background: After noting a significant reduction in aggression and agitation in treatment-refractory patients with molindone augmentation in severely aggressive inpatients, the authors conducted a retrospective medical records review to assess the possible anti-aggressive role of molindone treatment in a larger cohort of treatment-refractory inpatients. **Method:** Twenty-four weeks of data from thirty inpatients who were consecutively augmented with molindone, including progress notes, orders for seclusion, chemical restraint, and scores on the Agitation-Calmness Evaluation Scale (ACES) were systematically collected. The number of seclusions, number of as-needed medications (PRNs) and ACES scores were used to tabulate the frequency of aggression and agitation episodes during the 8-week period before, 8 weeks after, and 9 through16 weeks after the initiation of molindone augmentation treatment. **Results:** Over the observation period of twenty-four weeks, the number of episodes of PRN medication administration for agitation and aggression significantly decreased during molindone treatment, the degree of agitation significantly improved, and there was a nonsignificant trend effect of reduction of the number of seclusion episodes. The mean dose of molindone used was 186 mg. **Conclusions:** These data suggest a role for molindone augmentation in the treatment of persistently aggressive patients with severe treatment-refractory psychosis. The authors propose possible reasons for this effect and suggest that controlled studies are needed to substantiate these preliminary results.

Key Words: Schizophrenia, Antipsychotic, Aggression, Molindone, Agitation

Introduction

Chronic aggressive behaviors in persistently psychotic patients frequently lead to prolonged psychiatric inpatient stays, intrusive treatment interventions and staff injuries (1, 2). Difficulty in controlling such behaviors can impede discharge planning more than any other aspect of illness. Treatments that can reduce persistent aggressive behavior and associated agitation are key components of helping patients leave the hospital and return to the community.

Following the CATIE and CUtLASS studies demonstrating comparable efficacy between some first-generation (FGA) and second-generation (SGA) antipsychotics (3, 4) and after noting a significant reduction in aggression and agitation in severely aggressive psychotic inpatients residing in a specialized unit after the use of the first-generation antipsychotic molindone, we have been interested in its anti-aggressive effects. Molindone hydrochloride, a dihydroindolone, is classified as a mid-potency antipsychotic. While most other FGAs antagonize D2 neurons in both the substantia nigra zona compacta (A9) and ventral tegmen-

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Clinical Implications

Our results suggest that molindone augmentation of ongoing antipsychotic regimens may be effective in reducing aggression in patients with persistent psychotic illness refractory to other pharmacological interventions. Despite its established antipsychotic efficacy, molindone appears to be underutilized in favor of other antipsychotics. For example, molindone accounted for less than 1% of all antipsychotic drug prescriptions written for Medicaid patients in 1995 (31). A more definitive answer to this suggested effect of molindone should come from a prospective, well-controlled study to examine molindone's anti-aggressive and anti-agitation effects.

tal area (A10) regions, molindone is a potent and selective antagonist of A10 D2 neurons in the ventral tegmental area, a property it shares with sulpiride and clozapine (5).

Clinically, molindone's anti-agitation and anti-aggression effects have been shown in children in a randomized, placebo-controlled trial, as well as in two open-label trials involving children with conduct disturbances (6-8). Molindone has been effective and well-tolerated by elderly patients for the treatment of agitation and psychosis at doses comparable to younger adults (9). It has also been effective in treating agitation and delirium in HIV+ patients unable to tolerate other antipsychotic agents (10). Our recently published case series (11) also suggested that molindone could be effective in aggressive behaviors.

The aim of the present report was to better characterize the response after molindone augmentation in patients with both persistent violent behaviors and treatment-refractory psychosis. We included in this review all consecutively initiated inpatients on molindone who were considered treatment refractory to multiple and extensive antipsychotic trials with SGAs and who were augmented by their clinicians with molindone for the treatment of recurrent aggressive behaviors.

Method

We selected twenty-four weeks of medical records data, which included nursing notes, psychiatric progress notes, medical orders for seclusion, and medical orders for chemical restraint with oral or parenteral anti-agitation treatment (PRN, as needed medication) to record observations of aggressive behaviors. For the assessment of agitation, we used the Agitation-Calmness Evaluation Scale (ACES) on the reviewed chart data to tabulate the intensity of agitation episodes. We selected 3 time periods across the 24 weeks for analysis: 8 weeks prior to molindone (baseline period), 8 weeks after molindone treatment start, and an additional 8 weeks from the 9th to 16th week after molindone treatment started (endpoint period).

Participants

All inpatients who were consecutively initiated on molindone augmentation by their clinician at a 340-bed tertiary care psychiatric center during the period of January 2007 to December 2007 were screened for inclusion into the study. The following criteria were used to include subjects from the study cohort: 1) age ≥18 and ≤65; 2) treatment resistant to two previous antipsychotic trials, defined as two different SGAs in the past at equal or higher than 400 mg of chlorpromazine (CPZ) equivalents for a period of at least six weeks treatment together with significant poor social and instrumental functioning; 3) a minimum of three months in the hospital after their admission prior to start of molindone (in order to exclude subjects who may have the majority of their agitation events during the initial hospitalization, thus, incorrectly attributing any improvements to molindone); 4) at least three months of molindone treatment; 5) absence of concomitant electroconvulsive therapy; and, 6) absence of major change in psychotropic medication during the time period of interest in order to reduce the likelihood of confounding the results with changes in other antipsychotic medications. Molindone was in all cases an augmentation intervention to the patients' current antipsychotic treatment regimens. The primary outcome measures were the number of seclusions, the number of PRNs, and the change in scores on the Agitation-Calmness Evaluation Scale (ACES) during the two observation periods after start of molindone augmentation.

Assessments

Demographic data such as *DSM-IV* diagnosis, age, gender and duration of current hospitalization were recorded from the patients' medical record. We gathered the date each patient was started on his or her treatment with molindone and duration, as well as the dose and duration of any other neuroleptics and mood stabilizers the patient was taking. We assessed the levels of agitation during the three time periods noted previously: 8 weeks prior to beginning molindone treatment (baseline period); 8 weeks after; and, from 9 weeks through 16 weeks after beginning treatment with molindone. Agitation was quantified by the number of PRNs patients received at the time of the agitation episode and the number of seclusion episodes for agitation and aggression during these time periods. Both the PRN pharmacological interventions and seclusion episodes were always

accompanied in the patients' medical record by extensive nursing staff descriptions of patients' specific aggressive and agitated states. The PRN interventions consisted mostly of ziprasidone 20 mg i.m. given after an aggressive and agitated episode had occurred. Therefore, the numbers of PRN and seclusion episodes were considered a reliable proxy for aggressive and agitated behaviors.

In addition, we used the physicians' progress notes to determine scores on the Agitation-Calmness Evaluation Scale (ACES). The ACES is a single-item, 9-point scale used to quantify the level of agitation of patients (score of 1=marked agitation, 4=normal, 7=marked calmness or light sleep, and 9=unarousable from sleep). Scores in the range of 4 to 8 were considered indicative of an effective therapeutic response without excessive sedation.

The mean number of each of these variables (PRNs, seclusions, and ACES scores) were compared longitudinally. Increased agitation and aggression were reflected by higher

Table 1 Demographics (n=30)

	Mean	SD	Median	Range
Age (years)	43.30	12.00	39.34	23.45–65.92
Molindone dose (mg)	185.83	55.20	200.00	75.00–250.00
Length of stay prior to start of treatment (months)	137.26	239.91	18.59	.58–976.08*
	Frequency	**%**		
Diagnosis				
Schizophrenia (all subtypes)	13	43.33		
Schizoaffective	14	46.66		
Bipolar	3	10.00		
Ethnicity				
African American	21	70		
Latin American	6	20		
Caucasian	3	10		
Gender				
Male	26	86.67		
Female	4	13.33		
Molindone dosing				
75 mg dose	2	6.7		
100 mg dose	4	13.3		
125 mg dose	1	3.3		
150 mg dose	1	3.3		
175 mg dose	1	3.3		
200 mg dose	10	33.3		
225 mg dose	7	23.3		
250 mg dose	4	13.3		

* It should be noted that 9 patients were hospitalized for >5 years (range=149.17–976.08) prior to start of molindone treatment; SD=standard deviation.

numbers of PRNs and seclusions, and lower scores on the ACES.

Chlorpromazine (CPZ) equivalents were used to record relative antipsychotic potencies of concomitant antipsychotic drugs, which were compared based on the defined daily dose (DDD) (12). The study was approved by the Nathan Kline Institutional Review Board.

Statistical Analysis

Repeated measures analysis of variance (ANOVA-RM) was used to compare continuous variables (number of PRNs and seclusions) for the pre-molindone time period to the molindone treatment period. Treatment effects were tested at a significance level of 0.05. The Bonferroni multiple-test correction method was used to ensure an experiment-wise error rate of 0.05 (two-sided). All categorical measures (the ACES measure was treated as a categorical measure with scores ranging from 1–7; no patients attained a score of 8 or 9) were analyzed using Fisher's exact test. Ninety-five percent confidence intervals were derived by calculating the difference between the estimated proportions, assuming the sample was derived from an independent distribution. The statistical package SPSS, Release 15.0, was used for all analyses.

Results

During the study period, 35 inpatients were initiated on molindone in addition to their current psychotropic regimen. Of these 35 patients (10.29% of entire inpatient population), 5 patients were removed who did not satisfy the inclusion criteria. Twenty- six (86.67%) of the 30 patients (male=86.67%; female=13.33%) had experienced seclusion episodes or PRN events either prior to or during molindone treatment. The study sample included 13 patients with a *DSM-IV* diagnosis of schizophrenia (all subtypes), 14 with schizoaffective disorder and 3 with bipolar disorder. Sixteen patients had received clozapine in the past, and 9 patients were still on it. The remainder had been discontinued from clozapine due to nonresponse. Table 1 presents further demographic characteristics of the study sample.

The dose distribution of molindone ranged from 75 mg/day to 250 mg/day (mean dose 185.83±55.20 mg) with 200 mg/day being the most commonly prescribed dose (n=10; 33.3%) (See Figure 1). The mean duration of molindone treatment was 25.04 weeks; 76.67% (n=23) were also treated with mood stabilizers. All patients were treated concomitantly with their previously started antipsychotic: 80% (n=24) were treated with SGAs only; 14.29% (n=4) were currently treated with FGAs only; and, 7.14% (n=2) were treated with both an FGA and an SGA (see Table 2 for distribution of concomitant medications). The concomitant chlorpromazine antipsychotic equivalency was 943.43 mg (±570.18) average daily dose, ranging from 200 to 2,500 mg daily. As the sample size was diverse in terms of the distribution of antipsychotic medications, no statistical comparisons were conducted.

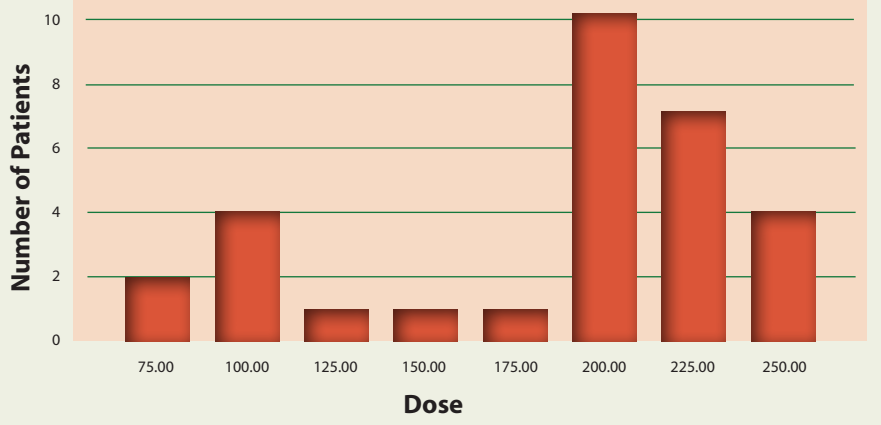
Table 2 Distribution of Concomitant Medications (n=30)

Antipsychotics	Frequency	%
Clozapine	9	30.00
Quetiapine	13	43.33
Haloperidol	5	16.67
Haloperidol Decanoate	4	13.33
Aripiprazole	1	3.33
Risperidone	1	3.33
Olanzapine	1	3.33
Chlorpromazine	1	3.33
Other Psychotropics:		
Depakote	13	43.33
Lithium	7	23.33
Clonazepam	10	33.33
Lamotrigine	1	3.33
Fluvoxamine	1	3.33
Venlafaxine	1	3.33
Trileptal	1	3.33

Note: the total number of patients on antipsychotics is >30 as some patients were on two antipsychotics.

There was a statistically significant reduction noted from baseline (pre-molindone) to endpoint (week 9–week 16) in number of PRNs administered (F [1, 29]=6.295, p=.018). The number of seclusion episodes showed a non-significant trend toward reduction (F [1, 29]=3.237, p=.082) (see Table 3). It should be noted that during the baseline period prior to molindone treatment, 20 patients did not receive any seclusion; thus, the study may have been underpowered to detect differences in seclusion rates as a result of molindone use. Nonetheless, of the 10 patients who did have seclusion episodes (n=33.33%), 9 experienced a reduction in the number of seclusions over the measured time interval (total number of seclusions at baseline=34; at 8 weeks=11; and, at 16 weeks=5), representing an important numerical reduction in the expected direction.

Figure 1 Distribution of Molindone Doses Across Patients

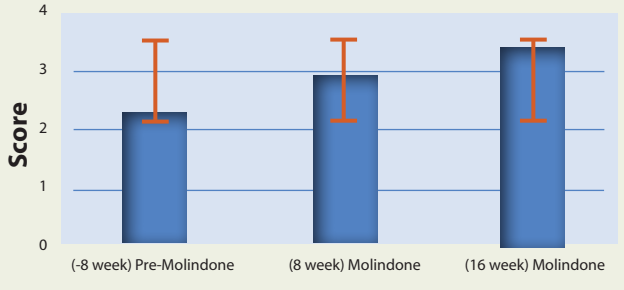


While 88.33% of patients had ACES scores ≤3 (indicating mild to marked agitation) at baseline, after 8 weeks of treatment with molindone only 70% of patients had ACES scores ≤3, and from 9 weeks to 16 weeks after treatment only 40.00% of patients exhibited mild to marked agitation (see Figure 2). Fisher's exact test was used to compare baseline ACES scores to 8 weeks after starting molindone and from 9 through 16 weeks after starting molindone. Results showed a significant difference in ACES scores between baseline period to 8 weeks (range: 1 to 6 points; Fisher's exact test ([1]=24.162, p=.001), and ACES scores between baseline and week 9 through week 16 (range: 1 to 7 points; Fisher's exact test [1]=16.339, p=.040) (see Table 3 and Figure 3).

To investigate any possible dose response of the effect of molindone, patients on molindone >200 mg daily (n=11) were compared to patients on ≤200 mg (n=19) daily and the number of PRNs received. Patients with doses of >200 mg daily experienced 63.81% (n=7.37) reduction in the number of PRNs administered and, similarly, patients with ≤200 mg daily doses experienced 69.27% (n=1.42) reduction in the number of PRNs administered; interactions between the actual milligram-per-milligram dose administered and the number of PRNs within subjects were not statistically significant (F[1, 28=2.179, p=.151]).

Of the thirty patients in our molindone-treated sample, 7 (23.33%) were discharged from the hospital 9.29 (±4.75) months after starting molindone treatment. Additionally, 28 (93.33%) patients remained on molindone after the endpoint of the study period, and all 7 discharged patients continued molindone treatment after discharge from the psychiatric facility.

Figure 2 ACES Scores Before and After Molindone Treatment



ACES=Agitation-Calmness Evaluation Scale (an increase in ACES score means improvement of agitation)

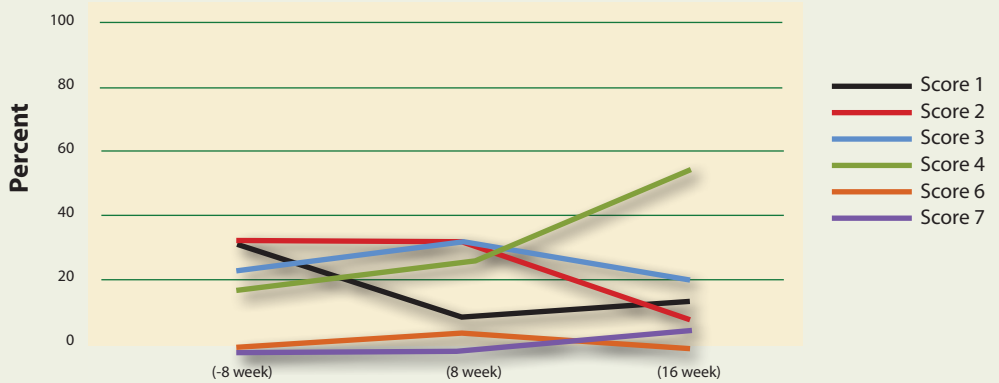
Side Effects

Side effects were limited to the occurrence of extrapyramidal side effects in one patient (mild akathisia, evidenced by restless pacing) noted at week 8 of treatment; this patient continued treatment to week 16 and completed the study. One patient reported dizziness and drowsiness after 8 weeks of treatment; however, the patient remained on molindone with no further incidents. It was, therefore, not felt that this adverse event was related to molindone. Augmentation with molindone did not produce any statistically significant change in weight (F [1, 27]=.010, p=.920). The mean weight 8 weeks prior to the start of molindone (195.32 lbs [±48.0]) decreased minimally after 8 weeks of treatment to 193.86±47.1 lbs, but increased back to 195.54±45.5 lbs by 16 weeks.

Discussion

Our retrospective chart review of the anti-aggression and anti-agitation effects of molindone used as an augmentation agent in inpatients with persistent aggressive and psychotic behaviors demonstrated a positive effect of molindone on aggressive behaviors. We found that, over an observation period of sixteen weeks, the number of episodes of PRN medication administration for agitation and aggressive epi-

Figure 3 Distribution of Scores for Agitation-Calmness Evaluation Scale



sodes significantly decreased during molindone treatment, that the degree of agitation significantly improved, and that there was a trend effect of reduction of the number of seclusion episodes. The anti-aggressive effect of molindone was progressive and increasing over the two observation periods after the initiation of molindone. This slow time course was seen for all three measures (number of PRNs, number of seclusions, ACES scores) and may have been in part a reflection of the extended time intervals of our assessment time points rather than a reflection of pharmacodynamic factors.

Unlike prior studies (13, 14), we did not observe any significant weight reduction; this, however, is still an important finding. Comprehensive analyses of widely used SGAs such as clozapine, risperidone, olanzapine and quetiapine have consistently indicated considerable weight gain with prolonged use (15). Molindone is unique in not having an effect on weight, which can be highly beneficial for patients' compliance and minimizing health risks.

We cannot assert whether this observed anti-aggressive effect appears to be part of, or separate from, the antipsychotic action of molindone, as we did not have any systematic measures of psychotic symptom change during the molindone-observation period. A review of medical chart notes written by the treating psychiatrists did not show major symptomatic change in psychosis states of these patients. We also cannot discount an effect due to regression to the mean over time in this group of treatment-refractory patients. However, we believe this is unlikely since most of our patients had been treated adequately, but unsuccessfully, for aggressive behaviors for a prolonged period of time before the start of molindone augmentation. In addition, these patients had been exposed to a combination of different antipsychotics and sodium valproate over a prolonged pre-study period as inpatients without satisfactory response; 83% of patients had either received clozapine in the past or were concomitantly taking clozapine, which had not controlled these behaviors, further reflecting the treatment refractoriness of these patients.

Regarding other anti-aggressive treatments, our group has shown that clozapine has superior effects on aggressive behaviors compared to risperidone, olanzapine and haloperidol (16). Sodium valproate has also shown significant efficacy for aggressive behaviors when used as an adjunctive therapy in patients with organic brain syndromes, dementia, mental retardation and psychotic disorders (17). However, a more recent study has indicated the limited usefulness of sodium valproate as a combination treatment for patients with acute schizophrenia (18). All patients included in the present study have been treatment refractory to clozapine's anti-aggressive effects, and many, as well, to trials of sodium valproate.

Molindone hydrochloride is structurally distinct from the other classes of FGAs such as the phenothiazines, the butyrophenones or the thioxanthenes. Clinically, it appears to function as a mid-potency antipsychotic, with 2 mg molindone clinically equivalent to 1 mg trifluoperazine (19, 20). However, receptor studies have demonstrated that molindone has much less affinity for D2 receptors in the striatum, ventral tegmental area, and nucleus accumbens compared to both haloperidol and chlorpromazine. Furthermore, postmortem samples of human caudate nucleus have shown that, of seventeen neuroleptics examined, only promazine and clozapine had less affinity than molindone for D2 receptors in this area. In contrast to other FGAs, which cause both a decrease in the number of spontaneously active dopaminergic neurons in the substantia nigra zona compacta (A9) and the ventral tegmental area (A10) with prolonged use, prolonged use of molindone only deactivates the A10 D2 system. Whereas inactivation of the A10 D2 neurons may be related to antipsychotic efficacy, inactivation of the A9

Table 3 Changes in Outcome Measures

	-8 Week		8 Week		16 Week		Partial Eta Squared	Observed Power	ANOVA
	Mean	SD	Mean	SD	Mean	SD			
PRNs	5.53	8.81	3.83	6.43	1.93	3.30	.178	.679	F(1, 29)=6.295, p=.018
Seclusions	1.20	3.04	0.37	0.99	0.17	0.65	.100	.413	F(1, 29)=3.237, p=.082
ACES	2.27	1.08	2.87	1.13	3.37	1.27	.316	.942	F(1, 29)=13.376, p=.001
Weight	195.32	48.05	193.86	47.08	195.54	45.52	.000	.051	F(1, 27)=.010, p=.920
	n	%	n	%	n	%	Chi Square		
ACES									
1	9	30.00%	3	10.00%	4	13.33%			
2	9	30.00%	9	30.00%	2	6.67%	Fisher's Exact Test (1)=24.162, p=.001 for (-8 Week) and Week 8		
3	7	23.33%	9	30.00%	6	20.00%			
4	5	16.67%	8	26.67%	16	53.33%	Fisher's Exact Test (1)=16.339, p=.040 for (-8 Week) and Week 16		
6	0	0.00%	1	3.33%	0	0.00%			
7	0	0.00%	0		1	3.33%			

SD=standard deviation; PRNs=number of as needed medications; ACES=Agitation-Calmness Evaluation Scale

D2 neurons is related to the development of extrapyramidal symptoms. Molindone's relative sparing of this system is a property it shares with SGAs such as clozapine and sulpiride. Animal studies have shown that antipsychotic blockade of A9 neurons can facilitate aggressive behaviors (21), whereas anatomically specific antipsychotic blockade of A10 D2 neurons can inhibit them (22, 23). This anatomically selective inactivation of A10 D2 neurons may account for the anti-aggressive properties of both molindone and clozapine. Molindone may possibly offer anti-aggressive properties similar to those of clozapine, which has demonstrated clear anti-aggression effects in several studies (16, 24-27).

However, it is difficult to fully understand why molindone, a drug putatively similar to clozapine, is working for aggression and agitation in patients who have failed clozapine. Clozapine's anti-aggression properties can be separated from its sedation effect or from its efficacy at reducing psychotic symptoms (28). The etiology of aggressive behavior is likely heterogeneous (29), and the efficacy of other agents in reducing aggression may rely on treating psychotic symptoms or cognitive deficits, rather than a primary effect on aggression itself. For example, the efficacy of olanzapine in reducing aggression was associated with improvements in neurocognitive function whereas clozapine's significant anti-aggression effect was not (30). A separate anti-aggression mechanism distinct from treatment of psychosis might account for why patients in our study who had failed clozapine presumably for lack of antipsychotic efficacy nonetheless showed reduced aggression with molindone augmentation.

Molindone was overall well-tolerated, with only one patient experiencing extrapyramidal side effects. It has essentially no affinity for muscarinic acetylcholine receptors in the caudate nucleus, and very little affinity for histamine H1 receptors or adrenergic α-1 receptors in the frontal cortex, which may underlie its low side-effect profile, including the absence of a sedative effect.

Limitations of our study are the retrospective and open-label design, which may have introduced significant rater and observer bias. In addition, the underlying other antipsychotic treatments were very heterogeneous and could not be controlled with the present design, introducing potential variance in our results. It is, therefore, possible that the use of concomitant medications other than molindone may have been related to this improvement. However, we took care to only include patients who had been inpatients for at least three months prior to the start of molindone in order to allow time for these concomitant medications to reach their full effect. All patients were considered treatment resistant on these concomitant medications based on well-established criteria. We also removed patients whose concomitant medications were changed substantially during the time period under analysis. An anti-aggressive effect due to acute hospitalization in a controlled environment is also less likely in

explaining these effects as we excluded recently admitted patients who were still highly agitated and aggressive during their immediate post-admission state. Other effects, which should be considered, are nonspecific effects of concomitant, nonpharmacological treatments (e.g., individual and group psychotherapy, therapeutic milieu). However, all included patients were exposed to the same therapeutic environment before and during the molindone-treatment phase, which consisted of a twenty-hour, weekly rehabilitative program and regular individual therapist contacts. Finally, a nonspecific sedative effect due to molindone or the medication combination could also have contributed to this improvement, although we did not observe sedative effects during molindone treatment as noted in the medical progress notes by the clinicians and our ACES measures.

Conclusions

Our results suggest that molindone augmentation of ongoing antipsychotic regimens may be effective in reducing aggression in patients with persistent psychotic illness refractory to other pharmacological interventions. Despite its established antipsychotic efficacy, molindone appears to be underutilized in favor of other antipsychotics. For example, molindone accounted for less than 1% of all antipsychotic drug prescriptions written for Medicaid patients in 1995 (31). A more definitive answer to this suggested effect of molindone should come from a prospective, well-controlled study to examine molindone's anti-aggressive and anti-agitation effects.

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