Data supplement for Krakowski et al., The Importance of Conduct Disorder in the Treatment of Violence in Schizophrenia: Efficacy of Clozapine Compared With Olanzapine and Haloperidol. Am J Psychiatry (doi: 10.1176/appi.ajp.2020.20010052)

Supplemental Methods Section on Treatment.

All procedures in the study were administered in a double-blind fashion. The 12-week trial consisted of two phases: a 6-week fixed-dose period (Phase I) and a 6-week variable-dose period (Phase II). During the first 6 weeks of the study, the fixed dose period, the prestudy antipsychotic was gradually discontinued while the doses of olanzapine, clozapine, and haloperidol were escalated to their target levels. The target doses were 20 mg/day for both olanzapine and haloperidol and 500 mg/day for clozapine. The doses were increased gradually over a week for olanzapine and haloperidol and over 24 days for clozapine. These doses remained fixed until the end of the first study period.

During the last 6 weeks of the study (Phase II), antipsychotic dose was allowed to vary within the following ranges: clozapine, 200 to 800 mg per day; olanzapine, 10 to 35 mg per day; and haloperidol, 10 to 30 mg per day. As the psychiatrists were blind to treatment group assignment, they could change the doses by prescribing various "levels" of medication.

The doses that were selected as target doses mentioned above are considered moderately high to high for all three medications[31, 32]. We used such doses because we did not want to risk the possibility of undertreatment in this repeatedly violent population. The meta-analysis study by Faay et al.[7] found that second-generation antipsychotics had greater antiaggressive effects than first-generation antipsychotics only when higher doses were used. The dosages reported in that study were in line with those chosen in our study. In addition, the dosage regimen in our study is similar to the one used in a major study of head-to-head comparisons of first and second-generations antipsychotics, which included olanzapine, clozapine and haloperidol[33].

During the study, the treating psychiatrists (who were blind to antipsychotic treatment assignment) were allowed to prescribe open-label lorazepam, diphenhydramine hydrochloride, or chloral hydrate as needed (prn) for agitation or disruptive behavior.

Supplemental Methods Section on Measures

For the Modified Overt Aggression Scale (MOAS), research personnel interviewed the research ward nursing staff after each shift to find out if any incident of overt aggression had occurred and to obtain detailed information for rating these incidents. The assaults were rated using the three categories of external aggression on the MOAS[34]: physical aggression against other people, verbal aggression, and physical aggression against objects. Physical aggression could vary from swinging at people (without any actual contact) or grabbing at clothing (a rating of 1) all the way to attacking others and causing serious injuries (a rating of 4). Verbal aggression could vary from mild curses or personal insults (a rating of 1) all the way to clear threats of violence towards others (e.g., "I will get you for this!" a rating of 4). Physical aggression against objects could vary from slamming doors angrily or making a mess (a rating of 1) all the way to setting fires or throwing objects dangerously (a rating of 4).

The total score for each type of assault represents the number of incidents over time as well as their severity. The overall Total MOAS score was obtained by assigning a different weight for each type of assault, using a psychometrically validated method developed by the MOAS authors[34]. The overall total score represents the number of incidents over time, their severity and the type of assaults.

The MOAS total score and the MOAS Physical Assault score were the two measures of efficacy. Interrater reliability, estimated by intraclass correlation coefficient (ICC), for the MOAS was established prior to the study and intermittently throughout the study. It was high throughout with ICC above 0.90.

The Positive and Negative Syndrome Scale (PANSS)[4] was used to assess clinical symptoms. Five factors were used as determined by a factor analysis study[35]: Positive Symptoms, Negative Symptoms, Excitement, Cognitive Impairment and Depression.

The PANSS was administered at baseline and throughout the study. Two independent raters performed assessments at baseline, week 6, and week 12 (or endpoint). These paired ratings were also used for the assessment of interrater reliability. The ICC for the PANSS was above 0.90. For the analyses in this article, we used the baseline and endpoint values. We removed the Hostility item from the PANSS, as its rating is influenced by the presence of assaults.

Supplemental Results Section on Dosages of Medication and Additional Medications.

There were no significant differences in dosages between CD and NCD groups for any of the three medications in either phase (p>.1). We also looked at the change in dose during the flexible phase of the study by comparing the dose at the end of Phase I (fixed phase) to the dose at the end of Phase II (the flexible phase). There were no significant differences in either increase or decrease of dose between the CD and NCD groups in the haloperidol ($F=2.45$, $df=1,30$, $p=.13$), olanzapine ($F=0.09$, $df=1,32$, $p=.77$), or clozapine ($F=2.12$, $df=1, 30$, $p=.16$) groups.

These changes in dose during the second phase of the study were mostly driven by insufficient efficacy for the fixed dosages or the presence of side effects, and therefore do not represent an adequate design to examine 'dose-response' relationships. Nonetheless, we investigated the total MOAS score and the Physical Aggression score in each of the three medication groups as a function of dose change in Phase II as well as the conduct disorder grouping. We also included the interaction between these two variables. None of these analyses were significant (p>.1 in all analyses).

As mentioned above, lorazepam, diphenhydramine hydrochloride, or chloral hydrate could be prescribed open-label as needed (prn) for agitation or disruptive behavior. During the study 56.5% (26 out of 46) of the NCD patients and 54.2% (29 out of 53) of the CD patients received such medication as needed. The difference between the CD and NCD group is not significant ($\chi^2 = 0.03$, $N=99$, $p= 0.89$).

We looked also at the dual classification, i.e., medication groups and conduct disorder groupings. We conducted a logistic regression analysis with the prn status (number of patients who received medications for agitation or disruptive behavior versus those did not receive any) as the dependent variable and the medication group and conduct disorder status as the

independent variables. The interaction between these two variables was also included in the model. The results indicated no significant main effect for either medication group (Wald χ^2=1.21, N=99, p=.55) or conduct disorder status (Wald χ^2=0.13, N=99, p=.72). The interaction between medication group and conduct disorder status was not significant either (Wald χ^2=0.48, N=99, p=.79).

Supplemental Results Section on Psychiatric Symptoms.

Improvements in the PANSS Total scores were not significant for either the medication or the CD groupings ($p>.1$). There was an improvement of 2.4 (S.D.=14.4), 5.3 (S.D.=9.9), and 2.6 (S.D.=15.0) points for the patients in the clozapine, olanzapine and haloperidol groups respectively. The difference in improvement among the medication groups was not significant ($F=0.63$, $df=2,98$, $p=.54$). The improvement in PANSS Total score was 5.1 points (SD=13.8) for NCD patients and 1.8 (SD=12.1) for CD patients. This group difference was not significant either ($F=1.55$, $df=2,98$, $p=0.22$). Furthermore, the interaction effect between medication and conduct disorder grouping was also not significant ($F=0.44$, $df=2,98$, $p=.65$).

Similarly to the PANSS Total scores, improvements in the Positive Symptoms Factor scores were not significant for either the medication or the CD groupings ($p>.1$ for both). There was an improvement of 1.14, 1.20, and 0.24 points for the patients in the clozapine, olanzapine and haloperidol groups respectively. The difference among the three medication groups was not significant ($F=0.90$, $df=2,98$, $p=.41$). Improvements in the Positive Symptom Factor was 0.96 in the NCD group and 0.78 in the CD group. This difference was not significant either ($F=0.06$, $df=1,98$, $p=.80$). The interaction effect between the medication and conduct disorder groupings was also not significant ($F=0.36$, $df=2,98$, $p=.70$).

Table S1. Duration of stay in the study (weeks) and dosages of medication (mg/day) at the end of Phase I (end of the first six weeks) and Phase II (end of the second six weeks)

Medication group	CD group	Duration of stay in study (weeks)[1]		Dosage (mg/day)[2]			
				End of first period		End of second period	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Haloperidol	No CD	10.26	3.54	20.20	3.11	24.47	5.98
	CD	8.62	3.48	19.84	4.40	19.40	7.88
Olanzapine	No CD	11.53	1.25	20.60	2.77	25.00	6.27
	CD	9.90	3.59	19.89	1.82	23.42	6.25
Clozapine	No CD	9.42	3.70	446.73	121.80	525.89	186.28
	CD	11.10	2.17	500.50	63.82	552.50	112.95

Abbreviations: CD – conduct disorder

[1] There were no significant differences in duration of stay in the study among the three medication groups and between the CD and NCD (see text).

[2] The differences in doses from the end of the first phase of the study (fixed phase) to the end of the second phase (flexible phase) did not reach significance in any of the three medication groups (see text). There were also no significant differences between the CD and NCD groups in any of the 3 medication groups (see text).

Figure S1: Modified Overt Aggression (MOAS) total and Physical Assault scores for the three medication groups, haloperidol, olanzapine and clozapine, in patients with (CD) and without conduct disorder (No CD) (See also Table 2).

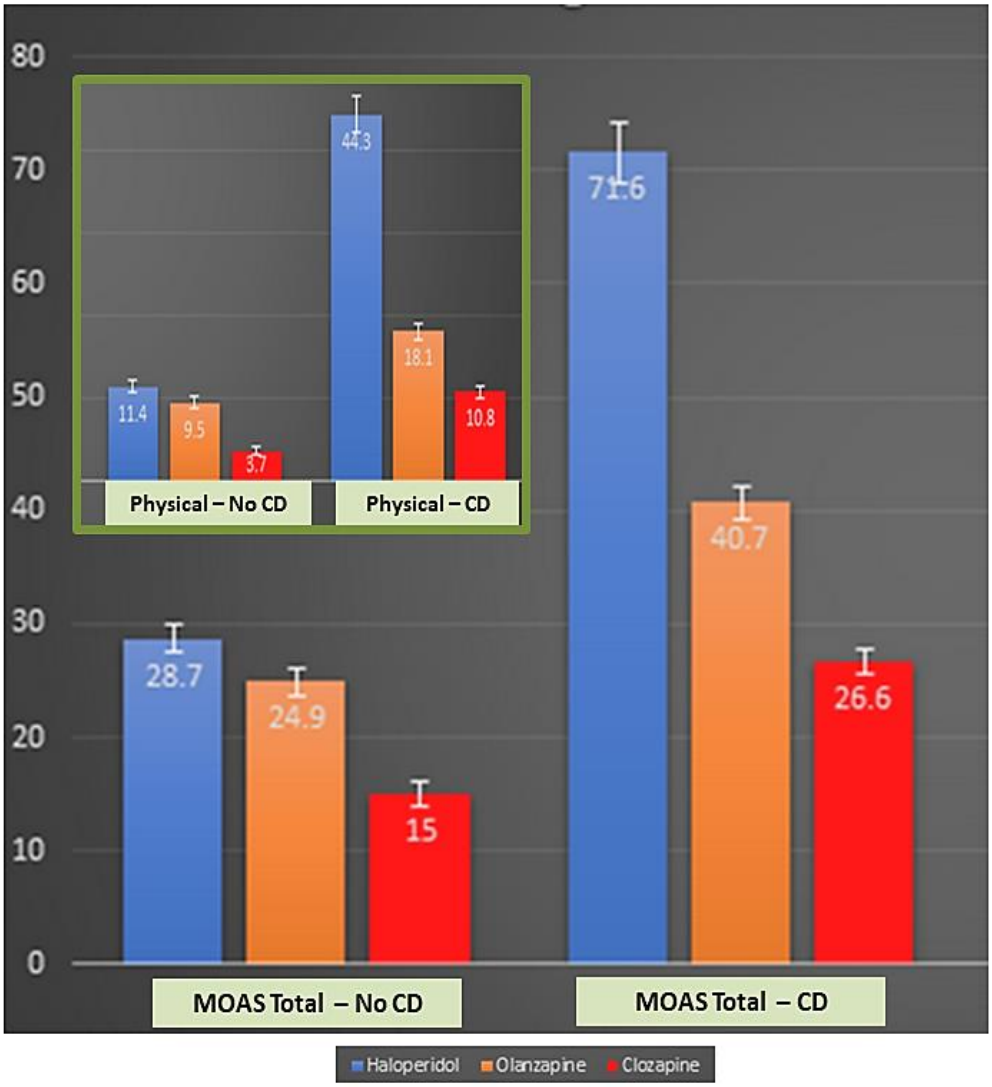

Figure S1 legend

The background figure provides information about the MOAS Total score for the three medications in the two subgroups, patients without conduct disorder and with conduct disorder.

The inlet figure provides information about the MOAS Physical Aggression score for the three medications in the two subgroups, patients without conduct disorder and with conduct disorder. For the group with conduct disorder all pairwise differences were significant after correction for multiple comparisons and multiple testing. For the group without conduct disorder the differences between olanzapine and haloperidol did not reach significance after correction for multiple comparisons and for multiple testing.