Efficacy of Dextromethorphan/Quinidine for Patients With Psychosis-Related Aggression: A Retrospective Case Series

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ABSTRACT

Background: Treatment-resistant aggressive behavior is a complex psychoneurological phenomenon with high health care and societal costs commonly observed in mental illnesses involving psychosis. Here, we report a preliminary evaluation of treatment with dextromethorphan/quinidine in 4 adult patients with significant history of psychosis-related aggression and impulsive behaviors.

Methods: The files of 4 inpatients with *DSM-5*–defined psychotic disorder and treatment-resistant aggression treated at the Oregon State Hospital (Salem, Oregon) between June and November of 2017 were retrospectively analyzed. The patients (age: mean ± SD = 59.8 ± 7.6) received open-label treatment with dextromethorphan/quinidine (final dose 20 mg/10 mg twice daily) for at least 12 weeks. Outcome was measured on the basis of patient self-report, treatment team evaluation, and physical examination by psychiatrists and primary care physicians.

Results: Three of the 4 patients were considered responders to dextromethorphan/quinidine based on clinical impressions of reduction in aggression and impulsive behavior. The nonresponder, who had a history of multiple traumatic brain injuries, showed mild improvement in agitation but continued to display impulsive self-harm behavior despite treatment. Dextromethorphan/quinidine was generally well-tolerated. No metabolic, gastrointestinal, or cardiovascular side effects were observed.

Conclusions: These preliminary findings support dextromethorphan/quinidine as a potential alternative to conventional regimens for treating aggression and impulsive behavior in patients with psychotic disorder. These results should be interpreted cautiously, as extended, double-blinded, placebo-controlled studies with a larger sample size are needed to validate findings from this retrospective case series.

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Aggressive behavior is one of the most important features of many psychosis-related illnesses, such as schizophrenia, dementia, and brain injuries, and often leads to significant social stigma, prolonged hospitalization, and increased health care and societal costs.[1,2] Aggression in psychosis is thought to be related to psychosocial causes, such as persistent delusion or hallucination, substance abuse, and cognitive disorientation,[3–5] but the precise neurobiological mechanism responsible for the psychopathological aggressive symptoms remains unclear, making treatment options for these patients limited.

A number of neurotransmitter systems, including serotonin (5-HT), dopamine, norepinephrine, and glutamate, are implicated in the pathogenesis of aggressive behavior.[6] With the presumed action on these neurotransmitter systems, common regimens for patients with psychosis-related aggression have mostly focused on lithium, antipsychotics (eg, haloperidol), and anticonvulsants (eg, valproic acid).[6,7] However, some patients can become resistant to these treatments.[8] Atypical antipsychotics with minimal extrapyramidal symptoms, such as clozapine, have been shown to be effective in reducing aggressive behavior in schizophrenia patients, making these medications a valid alternative for treatment-resistant patients.[9–11] However, these atypical antipsychotics have potential serious side effects, such as metabolic syndrome, cardiotoxicity, and agranulocytosis,[8,12,13] and may be contraindicated in some patients with significant predisposing risk factors. Thus, a different pharmacologic regimen with a milder side effect profile is highly desirable for patients who are treatment refractory or who develop significant adverse effects with other psychotropic medications.

Dextromethorphan is a common cough suppressant. But, we recently reported[14] initial success in treatment of agitation and aggression in a patient with frontotemporal dementia when used in combination with quinidine, which presumably increases dextromethorphan bioavailability via cytochrome P450 inhibition.[15,16] Here, we present a case series showing the effectiveness of the dextromethorphan/quinidine formulation in treating psychosis-related aggression and impulsive behavior over an extended period of time. Furthermore, we discuss the potential mechanism of this pharmacologic regimen.

METHODS

In this retrospective case series, the files of 4 patients with history of dementia, aggression, agitation, and impulsive or disinhibited behavior treated at the Oregon State Hospital (Salem, Oregon) between June and November of 2017 were analyzed. All psychiatric diagnoses were reevaluated and confirmed by certified psychiatrists at hospital admission using *DSM-5* criteria.[17] The patients were

Clinical Points

- Treatment options for psychosis-related aggression are associated with significant adverse effects.
- Current evidence suggests that dextromethorphan/quinidine is an alternative treatment with minimal adverse effects for psychosis-related aggression.
- The efficacy of dextromethorphan/quinidine in these cases suggests a glutamatergic mechanism underlying psychosis-related aggression.

white men with a mean ± SD age of 59.8 ± 7.6. Aggressive and impulsive symptoms had persisted in these patients despite multiple trials of anticonvulsant and antipsychotic drugs. The diagnoses, demographic information, treatment history with antipsychotic drugs, and rationale for treatment with dextromethorphan/quinidine are presented in Table 1.

The initiation of dextromethorphan/quinidine treatment and the evaluations of response were based on the clinical impression of patients' mood lability and the degree of aggressive behaviors after ruling out bipolarity. Dextromethorphan/quinidine was initiated at the daily dosage of 20 mg/10 mg and progressed to the final dosage of 20 mg/10 mg 2 times per day by the second week. Dextromethorphan/quinidine was maintained at the final dosage over 12 weeks or stopped if the patient developed adverse effects or targeted symptoms worsened (eg, patients showed increased aggression or agitation). All patients received 12-lead electrocardiogram (ECG) testing prior to initiating dextromethorphan/quinidine and dosage change and then monthly to monitor possible treatment adverse effects. The activity, diet, safety, and general well-being of the patients were recorded and assessed by clinical staff and attending psychiatrists daily. The changes in each patient's symptoms were evaluated and recorded by attending psychiatrists. The potential adverse effects were monitored by patient self-reports, nursing staff, and monthly physical examinations (eg, weight, blood pressure) and laboratory tests (eg, complete blood count and metabolic panel).

Concomitant psychiatric medications (Table 2) were titrated monthly based on symptoms or serum level. Patients who presented decreased target symptoms, which include verbal or physical aggression, paranoia, agitation, irritability, or number of seclusion events, while taking dextromethorphan/quinidine received a rating of "improved" and were considered responders. Those who showed no improvement on target symptoms or worsening symptoms received a rating of "no change" and were considered nonresponders.

RESULTS

The dextromethorphan/quinidine treatment responses are summarized in Table 2. Three of the 4 patients completed at least 12 weeks of treatment with dextromethorphan/quinidine.

In general, dextromethorphan/quinidine was well-tolerated, and all patients were compliant with treatment. No serious adverse effects were noted. Specifically, there were no cardiovascular side effects (eg, chest pain, palpitations, dizziness, or syncope) reported, and no significant change on ECG was noted compared to pretreatment baseline. There were also no gastrointestinal complaints (eg, diarrhea, constipation, nausea, abdominal discomfort) or weight changes noted.

The 3 treatment responders were continued on dextromethorphan/quinidine per patient records. One of the responders was initially diagnosed with schizophrenia due to persistent psychotic symptoms but later received the final diagnosis of frontotemporal dementia after review of recent neuroimaging evidence. All responders showed reduction in agitation, aggression, and impulsivity within 4 weeks of treatment initiation, with a decreasing number of behavioral interventions to control these behaviors. They also reported significant improvement in their mood and were able to start engaging in conversation with peers and staff. However, minimal changes were observed in their delusions and thought processes. All 3 responders were either discharged or

Table 1. Summary of Patient Demographics, Diagnoses, Treatment History, and Rationale for Dextromethorphan/Quinidine Trial

Patient No.	Age/Sex	*DSM-5* Diagnosis	Comorbid Conditions	Prior Treatments	Rationale for Dextromethorphan/Quinidine Trial
1	51 y/male	Frontotemporal dementia (presented with schizophrenia-like psychosis)	Chronic pain, hyperlipidemia, chronic obstructive pulmonary disease	Olanzapine, aripiprazole, citalopram, bupropion, quetiapine, lithium	Worsening physical and verbal aggression, extrapyramidal symptoms, lack of efficacy with multiple antipsychotic drugs
2	57 y/male	Schizoaffective disorder, dementia	Type II diabetes, hyperlipidemia, hypothyroidism, hypertension	Olanzapine, valproic acid, clonidine, quetiapine, perphenazine	Worsening physical and verbal aggression, lack of efficacy with multiple antipsychotic drugs
3	69 y/male	Schizophrenia, dementia, antisocial personality disorder	Chronic pain	Olanzapine, lorazepam, valproic acid, clonidine, haloperidol	Worsening physical and verbal aggression, lack of efficacy with multiple antipsychotic drugs
4	62 y/male	Schizophrenia paranoid type, dementia	Prior traumatic brain injuries, hepatitis C, chronic obstructive pulmonary disease, hypertension, hyperlipidemia	Olanzapine, aripiprazole, lorazepam, valproic acid, lithium, haloperidol	Increased aggression, agitation, impulsive self-harm behavior, lack of efficacy with multiple antipsychotic drugs

Table 2. Summary of Patient Responses to Dextromethorphan/Quinidine Treatment Including Concomitant Medications and Target Symptoms

Patient No.	Concomitant Medications	Target Symptoms	Treatment Response
1	Trazodone (200 mg qhs) Escitalopram (20 mg qam) Olanzapine (20 mg qhs)	Aggression, agitation, sexual disinhibition	Improved
2	Clonidine (0.1 mg bid) Perphenazine (8 mg qhs) Olanzapine (20 mg qhs)	Aggression, agitation, violent behavior toward staff and peers	Improved
3	Valproic acid (200 mg qam, 250 mg qhs) Haloperidol (125 mg IM every 4 wk) Clonazepam (0.25 mg qam, 0.5 mg qhs) Sertraline (30 mg qam) Olanzapine (10 mg qam, 30 mg qhs)	Aggression, agitation, violent behavior toward staff and peers	Improved
4	Fluoxetine (20 mg/d) Olanzapine (10 mg qam, 40 mg qhs) Lorazapem (0.5 mg qam, 2 mg qhs)	Aggression, agitation, impulsive self-harm behavior	No change

Abbreviations: bid = twice daily, IM = intramuscular, qam = once in the morning, qhs = once at night.

pending to be discharged to community care facilities, as they required a lower level of care after treatment with dextromethorphan/quinidine.

The patient who did not respond to treatment had a history of schizophrenia and multiple psychotic episodes and suicide attempts that required psychiatric hospitalizations. He had displayed increasing self-harm behavior under command hallucinations, which prompted his transfer to the Oregon State Hospital. His medical history is significant for comorbid hepatitis C and multiple traumatic brain injuries (TBIs). Although this patient showed mild improvements in agitation with the dextromethorphan/quinidine trial, his impulsive self-harm behavior continued to worsen. Dextromethorphan/quinidine treatment for this patient was discontinued.

DISCUSSION

The current case series describes our initial clinical impressions regarding treatment of aggressive and impulsive behavior secondary to treatment-resistant psychosis with dextromethorphan/quinidine in 4 inpatients. Our preliminary report[14] on the patient with frontotemporal dementia (patient 1 in Table 1) showed success in controlling aggression, agitation, and impulsive behavior (eg, binge eating, sexual disinhibition) within 2 weeks of starting dextromethorphan/quinidine treatment, and the benefit persisted beyond 12 weeks. This patient was discharged from the state hospital. Two inpatients with similar presentations who had previously failed multiple antipsychotic treatments also benefited from dextromethorphan/quinidine and were discharged from the hospital. Furthermore, dextromethorphan/quinidine at the recommended dosage (20 mg/10 mg twice a day) showed a minimal side effect profile, suggesting that this combination may be a safe and tolerable choice to treat behavioral dysfunction in this patient population.

The patient who failed to respond to dextromethorphan/quinidine provided some important insights into treatment considerations. This patient had suffered multiple TBIs prior to and throughout the evolution of his psychiatric condition, which could explain aggressive behavior[18] and comorbid psychiatric illnesses.[19,20] Previous neuroimaging studies have reported aggressive behavior to be associated with frontal lobe lesions in patients with prior head injuries,[21,22] a brain region implicated in modulating aggression-related circuits via the serotonergic and dopaminergic systems.[23] These findings are consistent with the notion that serotonergic abnormality may contribute to impulsive violence and aggression.[24–26] Interestingly, unlike patients with schizophrenia or dementia, there is insufficient evidence supporting the use of antipsychotic drugs to treat TBI-related aggression,[27] suggesting a different pathogenesis and psychopathology of the aggressive and impulsive symptoms in post-TBI patients, and may explain the lack of efficacy of dextromethorphan/quinidine in this patient with multiple TBIs. Another reason for the failure of dextromethorphan/quinidine and other psychotropic medications in this patient may be chronic hepatitis C, which has been linked to altered activity of cytochrome P450 (CYP) enzymes due to autoimmunity.[28] This change in CYP enzyme activity may have altered the pharmacokinetics of dextromethorphan/quinidine, potentially contributing to the lack of treatment response in this patient.

Taken together, the current study provides anecdotal evidence that supports the benefit of dextromethorphan/quinidine for treating aggressive behavior in patients with schizophrenia or dementia-related psychosis and sheds light on the potential neurobiology of aggression.

Mechanistic Implications

Aggression in patients with psychotic disorder is a complex phenomenon that can be influenced by, but not limited to, genetic, molecular, and neurologic factors. Interestingly, the pharmacology of dextromethorphan/quinidine seems to affect neurotransmitter systems linked with aggression.[29] Classically, the serotonergic neurotransmitter system has been implicated in aggressive behavior, with evidence demonstrating multiple 5-HT receptor subtypes associated with aggression in preclinical animal models and human studies.[24–26] In both in vitro and in vivo preclinical studies, dextromethorphan has been shown to increase synaptic 5-HT availability by inhibiting its reuptake.[29,30] Dextromethorphan/quinidine also affects other neurotransmitter systems associated with aggression, such as norepinephrine and glutamate.[6] While dextromethorphan inhibits norepinephrine reuptake, it is also a potent antagonist to glutamatergic *N*-methyl-D-aspartate (NMDA) receptors at the plasma levels achieved if combined with quinidine. This is consistent with the anti-aggression effect of valproic acid and memantine, both of which have the distinct mechanisms to reduce NMDA signaling.[31,32] However, while the

dopaminergic system is known to be involved in circuits relevant to aggression,[33] dextromethorphan/quinidine does not directly interact with dopamine receptors.[30] Thus, it is theoretically plausible that dextromethorphan/quinidine indirectly affects the dopaminergic system via its effects on the glutamate and 5-HT systems, potentially contributing to its efficacy in the treatment of aggression.[34]

Limitations

Since this study is a case series, it is limited by the nonblinded patient care teams and an uncontrolled experimental environment. The outcome mostly relied on self-reports or qualitative assessment by the patient care team, which lacks systematic and quantitative measurement of aggression (such as utilizing the Overt Aggression Scale[35]). Use of a range of concomitant medications in these patients, which was difficult to avoid due to the treatment-resistant nature of their conditions, could make interpretation of the efficacy of dextromethorphan/quinidine difficult. In addition, the small sample size and the length of treatment are also major limitations.

CONCLUSION

To our knowledge, this is the first case series to report efficacy of dextromethorphan/quinidine in the treatment of aggression and impulsive behavior in difficult-to-treat inpatients with psychosis. Although additional long-term, double-blind, placebo-controlled clinical trials are still required, the current case series suggests that dextromethorphan/quinidine may be a relatively safe and tolerable option to manage aggressive behavior if other agents such as lithium and antipsychotic or anticonvulsant medications fail. These data may also help basic scientists and clinical researchers design experiments to explore the pathophysiology and potential risk factors for psychosis-related aggression.

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REFERENCES

1. Fazel S, Grann M. The population impact of severe mental illness on violent crime. *Am J Psychiatry*. 2006;163(8):1397–1403.
2. McEvoy JP. The costs of schizophrenia. *J Clin Psychiatry*. 2007;68(suppl 14):4–7.
3. Ahmed AO, Richardson J, Buckner A, et al. Do cognitive deficits predict negative emotionality and aggression in schizophrenia? *Psychiatry Res*. 2018;259:350–357.
4. Fazel S, Gulati G, Linsell L, et al. Schizophrenia and violence: systematic review and meta-analysis. *PLoS Med*. 2009;6(8):e1000120.
5. Meyer JM, Cummings MA, Proctor G, et al. Psychopharmacology of persistent violence and aggression. *Psychiatr Clin North Am*. 2016;39(4):541–556.
6. Comai S, Tau M, Gobbi G. The psychopharmacology of aggressive behavior: a translational approach: part 1: neurobiology. *J Clin Psychopharmacol*. 2012;32(1):83–94.
7. Kane JM. Treatment programme and long-term outcome in chronic schizophrenia. *Acta Psychiatr Scand suppl*. 1990;82(S358):151–157.
8. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry*. 1995;152(2):183–190.
9. Samara MT, Dold M, Gianatsi M, et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. *JAMA Psychiatry*. 2016;73(3):199–210.
10. Spivak B, Mester R, Wittenberg N, et al. Reduction of aggressiveness and impulsiveness during clozapine treatment in chronic neuroleptic-resistant schizophrenic patients. *Clin Neuropharmacol*. 1997;20(5):442–446.
11. Spivak B, Roitman S, Vered Y, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. *Clin Neuropharmacol*. 1998;21(4):245–250.
12. Curto M, Girardi N, Lionetto L, et al. Systematic review of clozapine cardiotoxicity. *Curr Psychiatry Rep*. 2016;18(7):68.
13. Pramyothin P, Khaodhiar L. Metabolic syndrome with the atypical antipsychotics. *Curr Opin Endocrinol Diabetes Obes*. 2010;17(5):460–466.
14. Chen Q, Ermann A, Shad MU. Effectiveness of dextromethorphan/quinidine in frontotemporal dementia. *Am J Geriatr Psychiatry*. 2018;26(4):506.
15. Lutz JD, Isoherranen N. Prediction of relative in vivo metabolite exposure from in vitro data using two model drugs: dextromethorphan and omeprazole. *Drug Metab Dispos*. 2012;40(1):159–168.
16. Taylor CP, Traynelis SF, Siffert J, et al. Pharmacology of dextromethorphan: Relevance to dextromethorphan/quinidine (Nuedexta) clinical use. *Pharmacol Ther*. 2016;164:170–182.
17. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
18. Rao V, Rosenberg P, Bertrand M, et al. Aggression after traumatic brain injury: prevalence and correlates. *J Neuropsychiatry Clin Neurosci*. 2009;21(4):420–429.
19. Arciniegas DB, Harris SN, Brousseau KM. Psychosis following traumatic brain injury. *Int Rev Psychiatry*. 2003;15(4):328–340.
20. Jorge R, Robinson RG. Mood disorders following traumatic brain injury. *Int Rev Psychiatry*. 2003;15(4):317–327.
21. Grafman J, Schwab K, Warden D, et al. Frontal lobe injuries, violence, and aggression: a report of the Vietnam Head Injury Study. *Neurology*. 1996;46(5):1231–1238.
22. Tateno A, Jorge RE, Robinson RG. Clinical correlates of aggressive behavior after traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2003;15(2):155–160.
23. Seo D, Patrick CJ, Kennealy PJ. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. *Aggress Violent Behav*. 2008;13(5):383–395.
24. de Boer SF, Koolhaas JM. 5-HT1A and 5-HT1B receptor agonists and aggression: a pharmacological challenge of the serotonin deficiency hypothesis. *Eur J Pharmacol*. 2005;526(1–3):125–139.
25. Miczek KA, de Almeida RM, Kravitz EA, et al. Neurobiology of escalated aggression and violence. *J Neurosci*. 2007;27(44):11803–11806.
26. Takahashi A, Quadros IM, de Almeida RM, et al. Brain serotonin receptors and transporters: initiation vs termination of escalated aggression. *Psychopharmacology (Berl)*. 2011;213(2–3):183–212.
27. Plantier D, Luauté J; SOFMER group. Drugs for behavior disorders after traumatic brain injury: systematic review and expert consensus leading to French recommendations for good practice. *Ann Phys Rehabil Med*. 2016;59(1):42–57.
28. Obermayer-Straub P, Strassburg CP, Manns MP. Target proteins in human autoimmunity: cytochromes P450 and UDP-glucuronosyltransferases. *Can J Gastroenterol*. 2000;14(5):429–439.
29. Werling LL, Keller A, Frank JG, et al. A comparison of the binding profiles of dextromethorphan, memantine, fluoxetine and amitriptyline: treatment of involuntary emotional expression disorder. *Exp Neurol*. 2007;207(2):248–257.
30. Codd EE, Shank RP, Schupsky JJ, et al. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. *J Pharmacol Exp Ther*. 1995;274(3):1263–1270.
31. Basselin M, Chang L, Chen M, et al. Chronic administration of valproic acid reduces brain NMDA signaling via arachidonic acid in unanesthetized rats. *Neurochem Res*. 2008;33(11):2229–2240.
32. Wilcock GK, Ballard CG, Cooper JA, et al. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J Clin Psychiatry*. 2008;69(3):341–348.
33. de Almeida RM, Ferrari PF, Parmigiani S, et al. Escalated aggressive behavior: dopamine, serotonin and GABA. *Eur J Pharmacol*. 2005;526(1–3):51–64.
34. Johnson SW, Mercuri NB, North RA. 5-hydroxytryptamine1B receptors block the GABAB synaptic potential in rat dopamine neurons. *J Neurosci*. 1992;12(5):2000–2006.
35. Yudofsky SC, Silver JM, Jackson W, et al. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *Am J Psychiatry*. 1986;143(1):35–39.