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Evaluation of dextromethorphan with select antidepressant therapy for the treatment of depression in the acute care psychiatric setting

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Abstract

Introduction: Dextromethorphan (DXM), an *N*-methyl-D-aspartate receptor antagonist, may have ketamine-like antidepressant effects. Dextromethorphan is extensively metabolized via cytochrome P450 (CYP) 2D6, and its half-life in extensive metabolizers is 2 to 4 hours. The purpose of this study was to evaluate the effects of DXM in combination with a moderate-to-strong CYP2D6 inhibitor antidepressant on depression in an acute care psychiatric setting.

Methods: This was a single-center, retrospective chart review of adult patients with a depressive disorder diagnosis. Patients who received select antidepressant therapy with or without scheduled DXM were included. The primary outcome was the difference in time to improvement of depressive symptoms, which was an average composite of physician documentation, nurse documentation, and first time to 24 hours without as-needed anxiolytics or antipsychotics. The study group consisted of patients who received DXM with select antidepressant therapy, whereas the control group included those who received only select antidepressant therapy.

Results: A total of 40 patients were included. The median time to clinical improvement was 3.00 days and 2.83 days for the study group and control group, respectively ($P = .986$). The incidence of perceptual disturbances and delusions was higher in the study group as compared with the control group (55% and 35% vs 30% and 25%, respectively).

Discussion: Dextromethorphan was not associated with a rapid antidepressant effect. The commonly used dose of 30 mg daily may have been too low to have an effect; additionally, the most frequently utilized select antidepressant, bupropion, has moderately less CYP2D6 inhibition than fluoxetine and paroxetine.

Keywords: dextromethorphan, NMDA, depression, CYP2D6 inhibitor, bupropion, fluoxetine, paroxetine

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Introduction

Major depressive disorder is a leading cause of disability worldwide.[1] Currently, American Psychiatric Association[2] guidelines list cognitive behavioral therapy in combination with antidepressants as first-line therapy. These antidepressants are similar in their mechanisms of action, which target the monoaminergic system. Although considered equally effective, they have a delayed onset of clinical efficacy of weeks to months.[3] Despite effective treatment, approximately 40% of patients have treatment-resistant symptoms.[4] Therefore, there is a need to research

different depression pathways and medication mechanisms of action to bridge this gap.

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has shown rapid-acting antidepressant effects.[5-8] Dextromethorphan (DXM), an antitussive, may have ketamine-like antidepressant effects. Like ketamine, DXM is a noncompetitive, low-affinity NMDA receptor antagonist, sigma-1 receptor agonist, and serotonin transporter and norepinephrine transporter inhibitor.[3,9] Dextromethorphan is extensively metabolized via cytochrome P450 (CYP) 2D6. Its half-life in extensive metabolizers is 2 to 4 hours.[3] Therefore, in order to prolong its duration of action, it is paired with a strong CYP2D6 inhibitor, quinidine, in an approved product for pseudobulbar affect.

Advantages of DXM include its low cost and well-established side-effect profile.[10] Conversely, the DXM and quinidine combination product costs $1145 average wholesale price for a 1-month supply.[11] If effective, DXM could offer significant benefits to those suffering from depression due to its low cost and ease of administration as compared with current treatment options.

Currently, no controlled trials have investigated the antidepressant effects of DXM. However, an open-label, proof-of-concept trial showed well-tolerated, promising antidepressant effects of DXM in combination with quinidine in decreasing depressive and anxiety symptom severity when used for treatment-resistant depression.[12] Response and remission rates in the study were 45% and 35%, respectively.[12]

Current literature[12] suggests DXM has preliminary efficacy when combined with a CYP2D6 inhibitor. Additionally, providers at this institution have adopted this practice into their usual prescribing. Given the inconclusive nature of existing evidence, the objective of this study was to retrospectively evaluate the acute effects of DXM on depressive symptoms when combined with an antidepressant that is a moderate-to-strong CYP2D6 inhibitor compared with those same antidepressants alone in patients with depression.

Methods

Participants

This was a single-center, retrospective chart review of patients admitted to inpatient psychiatric units from January 1, 2014, to September 30, 2017. This study was approved by the Cleveland Clinic Akron General Institutional Research Review Board, and the requirement of informed consent was waived. Patients with a DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition) depressive disorder diagnosis as per ICD-9 or ICD-10 billing codes on discharge and who received select antidepressant therapy (ie, bupropion, fluoxetine, or paroxetine) with or without scheduled DXM were included.

Patients who received scheduled DXM in combination with bupropion, fluoxetine, or paroxetine were included in the study group (DXM group), whereas patients who received bupropion, fluoxetine, or paroxetine without DXM were included in the control group. A random number generator was used to select patients for inclusion into the control group, and matched random assignment was used to equate the groups on select antidepressant use. Patients who were under the age of 18, who had a discharge psychotic disorder diagnosis, who were currently pregnant or imprisoned, or who received DXM with a pro re nata (also known as as-needed) frequency were excluded.

The primary outcome was the difference in time to improvement of depressive symptoms defined as a composite average of time to first documented improvement by the psychiatrist, time to first recorded improvement by the nurse, and time to first 24 hours without as-needed anxiolytics or antipsychotics. Physician and nurse documentation were chosen as primary markers as they were less likely to be influenced by outside confounders as compared with another variable, such as length of stay, with which depression severity, insurance, housing, and other discharge complications could have confounded it. Also, to account for differences between physician and nurse documentation of improvement, the primary outcome was reported as an aggregate and as each individual component to show if these markers differed significantly. Use of as-needed anxiolytic or antipsychotic medication was chosen as a marker in an attempt to assess global improvement in terms of symptom severity because anxiety and agitation are assessed on depression scales, such as the Hamilton Depression Rating Scale.[13] The secondary outcomes were patient length of stay, as-needed anxiolytic or antipsychotic usage, incidence of psychotic symptoms, and rate of DXM discontinuation.

Data Collection

Baseline demographics were collected in addition to the following: physician and nurse documentation of depression improvement; as-needed anxiolytic or antipsychotic use; length of stay; incidence of DXM discontinuation; incidence of perceptual disturbances or delusions; dose, frequency, and formulation of DXM; and time of select antidepressant initiation.

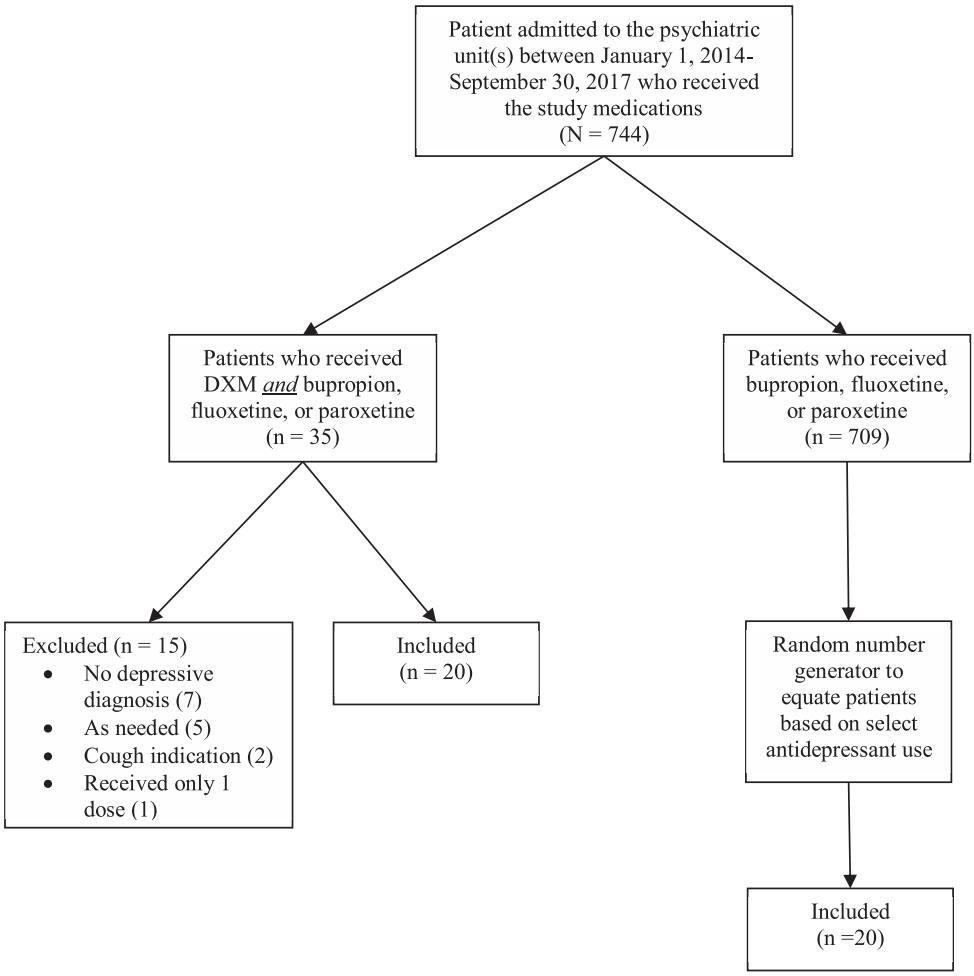

FIGURE: Description of study population selection (DXM = dextromethorphan)

Physician-documented improvement was defined as documentation in daily progress notes that indicated the patient had improved by use of the word(s): "improved," "getting better," "mood appears brighter," "is improving," "appears better," or "improved mood." Nurse assessment of improvement was defined as lack of the following documentation in the nursing assessment checklists at each shift change: suicidal ideation, self-harm, depressed, sad, and sullen mood and verbalized sadness, hopelessness, and loneliness for a 24-hour period. Anxiolytics included alpha 2-delta ligands, H_1 receptor antagonists, and benzodiazepines unless used for alcohol withdrawal. Collection of data started after the initiation of the study medications. Patients who received bupropion with fluoxetine or paroxetine were included in the fluoxetine and paroxetine groups, respectively, because they are stronger CYP2D6 inhibitors.[14-16]

Statistical Methods

Categorical variables were reported as number and proportion. Differences between groups were analyzed by chi-square or Fisher exact test as appropriate. Continuous variables were reported as mean with SD or median with interquartile range. Differences between groups were analyzed by Student *t* test or Mann-Whitney *U* test based on normality of data distribution. A nonparametric post hoc power analysis was performed to calculate the probability of a type II error for the primary outcome. Statistical analysis was performed using IBM SPSS statistics version 24.0 (IBM Corp, Armonk, NY), and a *P* value of less than .05 (2-sided) was considered statistically significant.

Results

There were 744 patients admitted to a psychiatric unit between January 1, 2014, and September 30, 2017, who had a depression diagnosis at discharge and received the study medications. Thirty-five patients received DXM during this time. Fifteen of these patients were primarily excluded due to receiving as-needed DXM or not receiving DXM for a depression indication (Figure). Therefore, 20

TABLE 1: Baseline demographic and clinical characteristics

Characteristic	Total (N = 40)	Control (n = 20)	Study (n = 20)	*P* Value
	Mean ± SD			
Age, y	37.3 ± 13.0	38.7 ± 13.8	35.8 ± 12.3	.487
	No. (%)			
Male	18 (45)	11 (55)	7 (35)	.204
Race				.108
White	36 (90)	16 (80)	20 (100)	
African American	3 (7)	3 (15)	0 (0)	
Other	1 (3)	1 (5)	0 (0)	
Depressive diagnosis				1.000
Depressive disorder	39 (97)	20 (100)	19 (95)	
Bipolar depression	0 (0)	0 (0)	0 (0)	
Other	1 (3)	0 (0)	1 (5)	
Lifetime history of suicide attempt	25 (62)	11 (55)	14 (70)	.327
Current substance abuse disorder	22 (55)	12 (60)	10 (50)	.525
Current anxiety disorder	24 (60)	11 (55)	13 (65)	.519
Current pain disorder	8 (20)	2 (10)	6 (30)	.235
Currently receiving ketamine	1 (3)	0 (0)	1 (5)	1.000
Currently receiving electroconvulsive therapy	1 (3)	0 (0)	1 (5)	1.000
Currently receiving antidepressant augmentation therapies	13 (32)	7 (35)	6 (30)	.736
>1 Select antidepressant				
Fluoxetine + bupropion	6 (15)	3 (15)	3 (15)	1.000
Select antidepressant initiation				.020
Home	9 (23)	8 (40)	1 (5)	
Inpatient	31 (77)	12 (60)	19 (95)	

patients were included in the DXM group and 20 patients in the control group by matched random assignment per select antidepressant use for a study total of 40 patients.

Baseline characteristics were similar between the study groups (Table 1). Of the 40 participants, most were white (90%) and female (55%) with an average age of 37 years. The majority had a lifetime history of a suicide attempt (62%), substance abuse (55%), and anxiety disorders (60%). Select antidepressant therapy initiation occurred significantly more in the inpatient setting for the DXM group versus the control group (95% vs 60%, respectively; $P = .020$).

Primary outcome results, reported as the composite and each individual component, are described in Table 2. There was no statistically significant difference in median time to depressive symptom improvement between the DXM group and the control group (3.00 days vs 2.83 days, respectively; $P = .968$). Time to physician documentation of improvement (2.50 days vs 4.00 days; $P = .327$) and time to first 24 hours without as-needed anxiolytic or antipsychotic use (2.00 days vs 3.00 days; $P = .398$) were shorter with DXM although not statistically significant.

For the secondary outcomes, patient length of stay was significantly longer in the DXM group (12.5 days vs 4.00 days, respectively; $P < .001$). Rates of as-needed anxiolytic (70% vs 55%) and antipsychotic (60% vs 35%) use, perceptual disturbances (55% vs 30%), and delusions (35% vs 25%) were higher in the DXM group but did not significantly differ from the control group.

The most common dose of DXM utilized was 30 mg daily (60%), and the most commonly used CYP2D6 inhibitor across both groups was bupropion (77%). The average duration of inpatient DXM use was 6.7 days.

Discussion

In this retrospective chart review, the effect of DXM on depressive symptoms, as-needed anxiolytic and antipsychotic use, and its overall tolerability were evaluated. Most study patients had a lifetime history of suicide attempt and a current anxiety disorder. Patients in the

TABLE 2: Summary of primary efficacy outcome in median days (interquartile range)

	Control (n = 20)	Study (n = 20)	*P* Value
Composite of average time to depressive symptom improvement	2.83 (1.75-4.58)	3.00 (1.67-5.00)	.968
Components of composite outcome			
Physician documentation of time to improvement	4.00 (2.00-5.00)	2.50 (1.00-4.75)	.327
Nurse documentation of time to improvement	3.00 (1.25-5.00)	4.00 (1.00-6.50)	.820
Time to first 24 h without as-needed anxiolytic or antipsychotic medication	3.00 (1.00-4.00)	2.00 (1.00-2.75)	.398

DXM group had a higher incidence of lifetime history of suicide attempt, anxiety disorders, use of salvage therapy (eg, electroconvulsive therapy and ketamine), and longer lengths of stay.

Dextromethorphan did not demonstrate statistical significance in decreasing time to depressive symptom improvement but appeared to be well tolerated overall. Although not significantly different, higher instances of perceptual disturbances and delusions were noted in the DXM group compared with the control group. Dextromethorphan did not appear to decrease as-needed anxiolytic or antipsychotic use or decrease length of stay.

There are several reasons why DXM may not have shown significant antidepressant activity in this study. One reason is that the most common dose used was 30 mg daily. The proof-of-concept trial used DXM doses up to 45 mg every 12 hours (90 mg daily).[12] It is likely that the dose utilized in this study was subtherapeutic and not able to produce antidepressant activity. In the present study, DXM was dosed once daily in all patients except for 1. However, dosing recommendations for the DXM combination product with quinidine and in the proof-of-concept trial recommend twice daily dosing.[12,17] This suggests that, depending on the agent, strong CYP2D6 inhibitors may only extend the half-life of DXM up to 12 hours. Finally, the most common CYP2D6 inhibitor used was bupropion, which had the least inhibitory action of the select antidepressants.[15,16]

Strengths of this study include contribution to the literature pool for the use of DXM in depression, the evaluation of DXM in combination with antidepressants that are moderate-to-strong CYP2D6 inhibitors, and the evaluation of DXM as a potential augmentation strategy. If effective, this would eliminate the need to use the combination product with quinidine, reducing the cost of therapy significantly. Also, due to its oral administration, it would serve as a patient-friendly salvage therapy option for those who have treatment-resistant symptoms.

There were limitations to this study. The results of the post hoc power analysis revealed a 95% chance of a false negative occurring due to the small sample size of the DXM group. Therefore, this study cannot definitively state that DXM did not produce antidepressant effects. The subjectivity of the primary outcome was another limitation. In this practice setting, validated depression scales were not used; thus, objective measurement of symptom severity and response to treatment was not possible. Retrospective design was also a limitation. Baseline depression severity and illness history could not be assessed, which limited evaluation of patient improvement. Another potential limitation was the subjective nature of psychiatrist documentation, increasing the risk of prescriber bias in the DXM group. The combination with nurse documentation and first time to 24 hours without as-needed anxiolytics or antipsychotics was used as an attempt to account for this limitation and make the primary outcome more robust. Finally, channeling bias was potentially present because it is probable that the DXM group was more likely to be prescribed DXM due to the refractory nature of their depression.

As previously mentioned, DXM possesses a complex pharmacology featuring NMDA receptor antagonism, sigma-1 receptor agonism, and effects on serotonin and norepinephrine transporters.[9] The NMDA receptor antagonism is the proposed mechanism of antidepressant activity although effects on these other receptors likely play a role as well. This proposed pathway, which differs from current treatments, offers promising benefit to those suffering from depression and requires further investigation. Future prospective studies should evaluate DXM at higher doses and use standardized scales to assess depression severity and detect response to therapy.

Conclusion

In this first retrospective chart review of DXM in depression in an acute care psychiatric setting, there was no difference in time to improvement of depressive symptoms in patients receiving DXM and those receiving standard antidepressant therapy. However, due to the aforementioned limitations, future studies should be conducted. Due to pharmacologic similarities between DXM and ketamine and results from a proof-of-concept

trial, DXM may still offer promising benefits to patients with depression.

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