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## Brief report

## The utility of the combination of dextromethorphan and quinidine in the treatment of bipolar II and bipolar NOS

Tammam Frederick Kelly<sup>a,b,\*</sup>, Daniel Z. Lieberman<sup>b</sup><sup>a</sup> Depression & Bipolar Clinic of Colorado, 315 West Oak Street, 5th Floor, Fort Collins, CO 80521, United States<sup>b</sup> Department of Psychiatry and Behavioral Science, George Washington University School of Medicine and Health Sciences, Washington DC, United States

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## ABSTRACT

**Background:** Dextromethorphan is an over-the-counter antitussive agent that may be a rapidly acting treatment for bipolar depression. Like ketamine, it is an NMDA receptor antagonist.

**Methods:** We conducted a retrospective chart review of depressed patients with treatment resistant bipolar II or bipolar NOS disorder who were treated with the combination of dextromethorphan 20 mg and quinidine 10 mg (DMQ). One pill of DMQ taken once or twice a day was added to participants' drug regimen. No changes were made to the pre-existing drug regimen during the course of treatment with DMQ. The primary outcome measure was the Clinical Global Impression-Improvement (CGI-I) score after 90 days of treatment.

**Results:** Seventy-seven participants met the inclusion criteria. All had been experiencing depressive symptoms for at least two years, and the mean number of failed medication trials was 21.2. The average CGI-I score at day 90 was 1.66 (1=slightly improved, 2=much improved). Some patients reported improvement within 1–2 days of starting DMQ. Nineteen patients discontinued treatment due to adverse effects, chiefly nausea.

**Limitations:** Because this was a retrospective chart review with no control group, conclusions about causation cannot be made. Nevertheless, the duration of depressive symptoms prior to starting DMQ makes spontaneous recovery less likely.

**Conclusions:** DMQ, an NMDA antagonist, may be effective in the treatment of bipolar depression. Because its putative mechanism does not depend on the monoaminergic system, it may be appropriate for patients who have not responded to other medications. Unlike ketamine, DMQ does not require IV administration.

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## 1. Introduction

There is a dearth of published research for treatment of bipolar II disorder and even less for Bipolar NOS. A commercially available combination medication, Nuedexta, contains dextromethorphan 20 mg and quinidine 10 mg (DMQ). This combination received FDA approval in 2011 for the treatment of pseudobulbar affective disorder. The quinidine was added to prolong the half-life of dextromethorphan through inhibition of the CYP2D6 liver enzyme metabolism. N-methyl-D-aspartate receptor antagonists have garnered interest in the treatment of the bipolar disorders and major depression (Zarate et al., 2010). Dextromethorphan (DM), a N-methyl-D-aspartate receptor antagonist, has gained interest for

treatment of bipolar disorders because of its similarity to ketamine and its ability to modulate glutamine (Tan III and Dubovsky, 2011). DMQ is currently being studied for the treatment of major depressive disorder (ClinicalTrials.gov, July 2013). Dextromethorphan alone has failed at least one treatment study for bipolar depression (Lapidus et al., 2013).

Both dextromethorphan and Quinidine have been in general medical use for over 60 years. Dextromethorphan was identified as an antitussive agent through a navy study funded by the Central Intelligence Agency that was seeking a non-addictive substitute for codeine (Defense, G.C.O.T.D.O, 1997). The FDA approved dextromethorphan as a prescription antitussive drug in 1954, and subsequently as an over-the-counter cough suppressant in 1958.

Quinidine is a class I antiarrhythmic agent. It is a stereoisomer of quinine, originally derived from the bark of the cinchona tree and has been in use at least as far back as 1749. The drug causes increased action potential duration, as well as a prolonged QT interval in the heart. When used to treat heart conditions the usual

\* Corresponding author at: Depression & Bipolar Clinic of Colorado, 315 West Oak Street, 5th Floor, Fort Collins, CO 80521, United States. Tel.: +1 970 484 5625; fax: +1 970 493 5131.

E-mail address: [TamKelly@comcast.net](mailto:TamKelly@comcast.net) (T.F. Kelly).

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dose is up to 300 mg four times a day. The highest daily dose of quinidine contained in Nuedexta is 60 times less than this, 10 mg bid.

## 2. Methods

The medical charts of the first 100 patients seen in a private mood disorders specialty clinic who were treated with DMQ for bipolar II disorder or bipolar NOS were reviewed retrospectively. To qualify for inclusion in the analysis patients either had to remain on DMQ for 90 days without any adjustment of other medications or have DMQ discontinued because of lack of efficacy, intolerable adverse effects or worsening of bipolar symptoms. Patients were included in the analysis if they had a primary diagnosis of bipolar II or bipolar disorder NOS, current episode depressed or mixed depression of two or fewer hypomanic symptoms based on clinical examination. The diagnosis of bipolar disorder NOS was based on meeting full DSM-IV criteria for bipolar II disorder except the required duration was reduced from four days to two (Akiskal, 2007). The length of their current episode was noted.

Patients selected for a trial of DMQ were chosen for clinical reasons chiefly because they had previously failed to attain stabilization with multiple trials of other medications. DMQ was added to patients' existing medications at a dose of one pill per day (dextromethorphan 20 mg, quinidine 10 mg). If no improvement was seen in the first three weeks it was increased to twice a day dosing. The one exception to the criteria for not changing medications was aripiprazole. Aripiprazole blood levels are increased by quinidine. Patients taking aripiprazole had their dose decreased by one third if DMQ dosing was once a day and decreased by one half if twice a day dosing was used.

The data were abstracted from the patient charts without identifying information.

Demographic data and history of current and previous medication trials were recorded. Treatment response was recorded at each appointment according to clinic routine using the Global Assessment of Functioning (GAF) scale and the Clinical Global Impression of Improvement scale (CGI-I):  $-3$ =very much worse,  $-2$ =much worse,  $-1$ =slightly worse,  $0$ =unchanged,  $+1$ =slightly improved,  $+2$ =much improved,  $+3$ =very much improved. The evaluation of the final CGI-I score was based on CGI-I scores at each visit, the Global Assessment of Functioning Scores (GAF) scores and by evaluation of patient questionnaires given before the start of each appointment as a matter of clinic routine. In this questionnaire, filled out just prior to the start of each appointment, patients self-rated depression and hypomanic symptoms, and recorded adverse effects. The final assessment was based on changes in mood, function and changes in stability.

Charts were examined for data relating to patients' discontinuation of DMQ including adverse effects, lack of response or worsening of bipolar symptoms. Family groupings were noted. Patients who stopped and restarted DMQ were noted. Data relating to the speed of improvement was noted if available.

This research is entirely self-funded.

Approval for the study was obtained from the institutional review board of the Poudre Valley Health System.

## 3. Results

The final average CGI-I score was 1.66 SD ( $n=59$ ).

Of the first 100 patients, 23 patients were excluded from further consideration: 12 because they failed to take DMQ and/or other medications prescribed to control their bipolar disorder, 8 patients because another psychotropic medication was started or

stopped with in the first 90 days of starting DMQ and 3 patients were lost to follow up.

All patients had at least two years of continuous or near continuous bipolar depression symptoms. Nineteen patients discontinued treatment with DMQ because of adverse effects. Gastrointestinal disturbance, chiefly nausea, were cited by 16 of the 19 patients. The adverse effects, while significant enough to stop DMQ, were not debilitating and resolved within 1–2 days of stopping DMQ. Eleven of 17 patients who discontinued due to adverse effects did so at a dose of one pill per day. The remaining 6 reached twice a day dosing. Aside from these 19 patients and the 3 who experienced worsening of bipolar symptoms, the rest of the patients tolerated DMQ well. None of the patients who stayed on DMQ reported any adverse effects or worsening of preexisting adverse effects.

Fifty-eight patients underwent a trial of DMQ showing an average CGI-I score of 1.66 SD 1.22. Three patients displayed minimum worsening of bipolar symptoms (CGI-I =  $-1$ ), two were more irritable; one experienced an increase in racing thoughts. These resolved within a day or two of stopping DMQ.

DMQ was stopped in 11 patients because of lack of improvement (CGI-I =  $0$ ), they all had reached twice a day dosing.

Three patients who experienced a favorable response to DMQ ( $+2$  CGI-I) discontinued DMQ for non-clinical reasons, 2 because of cost and one for unknown reasons. After discontinuing DMQ all three experienced worsening symptoms of depression. When DMQ was restarted they all regained their prior level of improvement. One of these patients, after stopping DMQ and becoming depressed again, tried to self-treat with over-the-counter dextromethorphan alone. He titrated up to 20 mg 4 times a day without relief and became sedated at the highest dose. There were two family groupings in the study. The first family grouping was a father, CGI-I =  $+3$  and son CGI-I =  $+2$ . The second grouping consisted of a father, son and daughter that all showing a CGI-I of  $+2$ . Two of the patients who stopped because of adverse effects indicated that they also saw improvement; each was on a dose of one pill a day.

The mean number of medication trials prior to starting DMQ was 21.2, SD 10.94. Of the patients who were assigned a CGI-I score the mean number of medication trials was prior to DMQ was 18.7 SD 8.71. Of the patients who stopped DMQ because of side effects the mean was 29.1 SD 13.39.

The mean age of participants was 47.2 years old (range 16–81). The correlation between age and change in CGI was not significant. There was no significant difference in response between the 28 men and 30 females. There is a nonsignificant trend ( $p=0.0665$ ) showing participants with bipolar II experienced a greater change in CGI compared to participants with bipolar NOS. The mean length of treatment at the Depression and Bipolar Clinic of Colorado was 5.0 years (range 1–18).

While no formal inquiry was made for the patients in the present study, a number of patients spontaneously remarked how rapidly DMQ worked, often within a day or two, of starting DMQ or when increasing it to twice a day dosing.

## 4. Discussion

This retrospective study suggests DMQ may have clinical utility in the treatment of patients who suffer from bipolar II and bipolar NOS disorders, at least in patients who had episodes that were refractory to multiple trials of medications. The discontinuation rate of 25%, due to adverse effects, may be of concern. However the patients in this study who dropped out because of adverse effects had an average of 29.1 SD 8.71 prior medication trials. Compared to the patients who stayed on DMQ or stopped because of lack of efficacy, the average was 18. It has been demonstrated in previous affective studies that the higher the number of previous failed

medication trials, the more likely that the future trials will fail (Rush et al., 2006).

The large number of patients discontinuing treatment with DMQ either because of adverse effects or possible exacerbation of bipolar symptoms brings up the possibility that doses of less than 20 mg of dextromethorphan a day may have clinical utility. The 11 patients who experienced no improvement at twice daily dosing may have benefited from a higher total daily dose of the dextromethorphan. This possibility should be further explored. A change of the dose of quinidine component could also be used to manipulate DM blood levels and yield better results.

Three patients suffered from a minor increase in bipolar symptoms when DMQ was started. The symptoms experienced were well within the range of changes the patients had previously experienced spontaneously.

The timing of the improvement, within a day or so by some patients suggests that this was directly caused by DMQ.

DM appears to have a mechanism of action similar to ketamine (Tan III and Dubovsky, 2011). Ketamine has been shown to have a rapid onset of action, within minutes of IV treatment, in at least two major depression studies and one bipolar study (Lapidus et al., 2013). Other studies of ketamine for affective disorder are underway (Lapidus et al., 2013, ClinicalTrials.gov, July 2013). DMQ may carry more promise for research as it is already FDA approved, does not have to be administered IV and carries a far less chance of abuse than ketamine does.

Like ketamine, another N-methyl-D-aspartate (NMDA) receptor antagonist effective in the treatment of depression, dextromethorphan belongs to a group of substances with psychoactive (dissociative) effects. When taken in large amounts, it produces effects similar to PCP, and is used recreationally primarily by young adolescents (Akerman et al., 2010). Compulsive users may experience tolerance and withdrawal symptoms that can include craving, diaphoresis, nausea, hypertension, and tachycardia (Martin and Jasinski, 1977).

Most reports of dextromethorphan abuse are anecdotal, so it is difficult to estimate the prevalence. Nevertheless, the risk appears to be quite low. Other addictive substances that are available over-the-counter, such as alcohol, caffeine and tobacco, are misused by millions of Americans. Dextromethorphan, in contrast, appears to have limited appeal for most individuals, and there has not been any action taken to restrict its availability. When prescribed therapeutically in the context of a doctor–patient relationship, the risks with regard to abuse are probably less than the risks associated with other commonly used psychiatric medications such as benzodiazepines, psychostimulants, or the atypical antipsychotic quetiapine. Dextromethorphan has been widely available as an inexpensive over-the-counter medication since 1958 and it has not led to wide spread abuse. Given the disabling nature of treatment-resistant depression, the risk of abuse is substantially outweighed by the potential benefits.

## 5. Limitations

This study was a retrospective chart review and is subject to all the limitations associated with an open-label, naturalistic, uncontrolled study design. This limitation is somewhat mitigated by the assignment of quantitative CGI-I scores, GAF scores and the patient's own standardized rating of multiple symptoms, all performed as a component of clinical care during each visit to the clinic. The data was collected by the lead author. DMQ was an add on medication so it is possible that the patients who experienced improvement did so as a result of the cumulative effects of other medications already prescribed. The length of continuous or near continuous severe symptoms for at least 2 years, however, make spontaneous improvement that lasted

90 days or more unlikely. The spontaneous off-on-off-on improvement experienced by 3 patients also support a cause and effect relationship.

The decrease of aripiprazole by one third if DMQ dosing was once a day and by one half if dosing was twice daily was based on a best-guess estimate of how quinidine affected the pharmacodynamics of aripiprazole. It is unknown if the final blood level of aripiprazole was higher or lower as a result of this. The change of blood level of aripiprazole could explain either the adverse effects, improvement or worsening of symptoms.

The worsening of bipolar symptoms, experienced by 3 patients, were well within changes in symptoms previously experienced by the patients and thus may not have been due to DMQ treatment. The average of 21.2 medication trials given prior to the start of DMQ is undoubtedly an underestimation. In reviewing the history of medications tried prior to joining the clinic, many patients were unable to remember all the medications that they had previously tried or if they had tried medications more than once. The long treatment history of many of the patients, some greater than 30 years, limited the ability to gather information from previous clinicians.

## 6. Conclusion

The combination of dextromethorphan and quinidine appears promising for the treatment of bipolar II and bipolar NOS disorders, at least in refractory patients. Further research with less refractory patients could clarify its potential benefit. More dosing choices could lead to better outcomes.

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### Conflict of interest

The authors have no conflicts of interest.

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