ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2020 April 19; 10(4): 29-80

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

Contents

Monthly Volume 10 Number 4 April 19, 2020

EDITORIAL

29 Evidence for using dextromethorphan-quinidine for the treatment of agitation in dementia
Tampi RR, Joshi P, Marpuri P, Tampi DJ

REVIEW

34 Moderators and mediators of antipsychotic response in delusional disorder: Further steps are needed
González-Rodríguez A, Guàrdia A, Palao DJ, Labad J, Seeman MV

ORIGINAL ARTICLE

Basic Study

46 Comparison of novel tools with traditional cognitive tests in detecting delirium in elderly medical patients
Meagher DJ, O'Connell H, Leonard M, Williams O, Awan F, Exton C, Tenorio M, O'Connor M, Dunne CP, Cullen W, McFarland J, Adamis D

Retrospective Study

59 Risk factors for depression in patients with chronic obstructive pulmonary disease
Yao HM, Xiao RS, Cao PL, Wang XL, Zuo W, Zhang W

META-ANALYSIS

71 Diagnostic accuracy and clinical utility of non-English versions of Edinburgh Post-Natal Depression Scale for screening post-natal depression in India: A meta-analysis
Russell PSS, Chikkala SM, Earnest R, Viswanathan SA, Russell S, Mammen PM

Contents

World Journal of Psychiatry

Volume 10 Number 4 April 19, 2020

ABOUT COVER

Editorial Board Member of *World Journal of Psychiatry*, Laura Orsolini, MD, MSc, PhD, Academic Research, Doctor, Senior Research Fellow, Psychopharmacology Drug Misuse and Novel Psychoactive Substances Research Unit, University of Hertfordshire, Hatfield AL109AB, Herts, United Kingdom

AIMS AND SCOPE

The primary aim of *World Journal of Psychiatry* (*WJP*, *World J Psychiatr*) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, forensic psychiatry, geriatric psychiatry, military psychiatry, neuropsychiatry, orthopsychiatry, psychoanalysis, and psychosomatic medicine.

INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Lu-Lu Qi*

Proofing Production Department Director: *Xiang Li*

Responsible Editorial Office Director: *Ruo-Yu Ma*

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
April 19, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2020 April 19; 10(4): 29-33

DOI: 10.5498/wjp.v10.i4.29

ISSN 2220-3206 (online)

EDITORIAL

Evidence for using dextromethorphan-quinidine for the treatment of agitation in dementia

Rajesh R Tampi, Pallavi Joshi, Padmapriya Marpuri, Deena J Tampi

ORCID number: Rajesh R Tampi (0000-0001-6754-6567); Pallavi Joshi (0000-0002-9622-4580); Padmapriya Marpuri (0000-0001-7407-4625); Deena J Tampi (0000-0002-4349-7622).

Author contributions: All authors equally contributed to this manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Manuscript source: Invited manuscript

Received: February 8, 2020
Peer-review started: February 8, 2020
First decision: February 17, 2020
Revised: March 3, 2020
Accepted: March 22, 2020
Article in press: March 22, 2020
Published online: April 19, 2020

P-Reviewer: Kotzalidis GD
S-Editor: Zhang L

Rajesh R Tampi, Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH 44106, United States

Rajesh R Tampi, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH 44195, United States

Pallavi Joshi, Department of Psychiatry and Behavioral Sciences, Northwell Health-Staten Island University Hospital, Staten Island, NY 10306, United States

Padmapriya Marpuri, Department of Psychiatry, Einstein Medical Center, Philadelphia, PA 19141, United States

Deena J Tampi, Diamond Healthcare, Richmond, VA 23219, United States

Corresponding author: Rajesh R Tampi, MD, Chairman, Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH 44106, United States. rajesh.tampi@yale.edu

Abstract

Behavioral and psychological symptoms including agitation are common in dementia, and are associated with decreased quality of life, increased risk of institutionalization, and greater patient and caregiver distress. Pharmacological agents used for management of behavioral and psychological symptoms of dementia are limited by their tolerability, prompting a need for identifying efficacious and safe pharmacological treatments for managing agitation in dementia. The combination of dextromethorphan and quinidine sulfate is approved for pseudobulbar affect, and may be effective in managing agitation in dementia. A review of literature found only one randomized controlled trial that evaluated the use of dextromethorphan-quinidine for the management of agitation in dementia when compared to placebo. Data from this trial demonstrated that dextromethorphan-quinidine decreased agitation in dementia, and was well tolerated. Although promising, further research is needed before dextromethorphan-quinidine combination can be accepted as a standard treatment for agitation in dementia.

Key words: Dextromethorphan; Quinidine; Agitation; Dementia; Behavioral and psychological symptoms of dementia

L-Editor: A
E-Editor: Qi LL

Core tip: Dextromethorphan-quinidine is approved for the treatment of pseudobulbar affect and may be effective in managing agitation in dementia. There is only one published trial that has evaluated the use dextromethorphan-quinidine for agitation in dementia. The study was of good quality and found that dextromethorphan-quinidine decreases severity of agitation when compared to placebo. Additionally, dextromethorphan-quinidine was fairly well tolerated and did not appear to cause significant sedation or worsen cognitive symptoms among individuals with dementia.

Citation: Tampi RR, Joshi P, Marpuri P, Tampi DJ. Evidence for using dextromethorphan-quinidine for the treatment of agitation in dementia. *World J Psychiatr* 2020; 10(4): 29-33
URL: https://www.wjgnet.com/2220-3206/full/v10/i4/29.htm
DOI: https://dx.doi.org/10.5498/wjp.v10.i4.29

INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are a group of psychological reactions, psychiatric symptoms and behaviors including agitation and aggression that are unsafe, disruptive, and impair the care of the individual in a given environment[1]. BPSD is seen in one-third of individuals with dementia who live in the community and in up to 80% of individuals with dementia who live in skilled nursing facilities[2]. The prevalence of agitation in dementia can be up to 46%, and is associated with decreased quality of life and increased risk of institutionalization for these individuals, in addition to greater caregiver burden and higher social and economic burden of caring for these individuals[3,4].

Non-pharmacological interventions are recommended as first-line for management of agitation in dementia. Pharmacotherapy including antipsychotics, antidepressants, anticonvulsants and cognitive enhancers are used when non-pharmacological interventions are ineffective[5]. Unfortunately, these medications are burdened with a significant side effect profile including QTc interval prolongation, weight gain, anticholinergic effects and cardiovascular adverse effects that carry substantial risks for the geriatric population[5]. Therefore, there is a great need for identifying efficacious and safe pharmacological treatments that are suitable for managing agitation in dementia.

Dextromethorphan is a low-affinity, uncompetitive N-methyl-D-aspartate receptor antagonist, σ1 receptor agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic α3β4 receptor antagonist[6]. Dextromethorphan has low and variable bioavailability when administered alone because of its rapid first-pass metabolism and subsequent elimination. The addition of quinidine, a potent inhibitor of the cytochrome P450 (CYP) liver enzyme CYP2D6, inhibits dextromethorphan metabolism and yields greater bioavailability[6]. The combination of dextromethorphan and quinidine sulfate is approved for the treatment of pseudobulbar affect in the United States and European Union. Evidence suggesting a potential effect of dextromethorphan-quinidine for agitation in dementia comes from controlled clinical trial data in non-demented patients with pseudobulbar affect[7].

The aim of this editorial is to review the literature on published randomized control trials (RCTs) that evaluated the efficacy and tolerability of dextromethorphan-quinidine for the management of agitation in dementia.

EVIDENCE FOR USIGN DEXTROMETHORPHAN-QUINIDINE FOR AGITATION IN DEMENTIA

A review of literature found only 1 RCT that evaluated the use of dextromethorphan-quinidine for the management of agitation in dementia (Table 1)[8]. The study was assessed as being of good quality based on JADAD criteria (Table 2). The details of the study are described in Table 3.

DISCUSSION

Available data from RCTs on the use of dextromethorphan-quinidine for the

Table 1 Summary of included studies

Ref.	Country of origin	Number of participants	Age (yr)	Setting	Comparators	Duration
Cummings *et al*[8], 2015	United States	220	50-90	Outpatient clinics, assisted living and nursing facilities	Dextromethorphan-quinidine *vs* placebo	10 wk

management of BPSD is extremely limited. The only trial that we found in our literature review evaluated the efficacy of dextromethorphan-quinidine in reducing severity of agitation among individuals with Alzheimer's disease when compared to placebo. This is the first dementia-related trial to use a sequential parallel comparison design[8]. In studies using this design, the first stage randomizes more patients to placebo than to active treatment. In the second stage, placebo non-responders from stage 1 are rerandomized and are included in the primary analysis. Pooled analysis of both stages maximizes the power to detect treatment differences and reduces the required sample size[8].

In this trial, treatment with dextromethorphan-quinidine demonstrated statistically significant decrease in agitation and aggression when compared to placebo. The reduction in agitation was considered clinically significant as measured by clinician rated scales. While the Alzheimer disease–related agitation characteristics of patients in this study were generally consistent with the International Psychogeriatric Association definition of agitation[8], patient emotional distress in patients was not directly measured.

Dextromethorphan-quinidine was generally well tolerated in this elderly population and was not associated with cognitive impairment. Most adverse events, including dizziness and diarrhea, were consistent with those observed in dextromethorphan-quinidine trials for pseudobulbar affect[8]. Falls were more common among patients receiving dextromethorphan-quinidine when compared to placebo. This may be explained by greater duration of exposure to dextromethorphan-quinidine and the lack of randomization to groups based on fall risk.

The strengths of the study include the use of the sequential parallel comparison design; inclusion of stable concomitant medications, including psychotropic medications, high retention rate, blinding of study sites to all aspects of the study, use of prespecified sensitivity analyses to corroborate the primary efficacy end point, and consistent results among multiple secondary outcomes and primary end point. Limitations of this trial include a short duration (10 wk), and a dose-escalation schedule that limited evaluation of dose-response relationships. Exclusion of concomitant drugs related to quinidine, tricyclic antidepressants, monoamine oxidase inhibitors, or phenothiazines, as well as cardiac parameters limit the generalizability of study findings. Finally, the patient population was predominantly outpatient, with only 5.5% of study participants domiciled in nursing homes. The treatment response may not be generalizable to patients in nursing homes and should be further explored.

In the study reviewed, the combination of dextromethorphan-quinidine was clinically efficacious for agitation and was generally well tolerated. However, evidence-based trials are limited, as is the generalizability of the results to wider clinical and nursing home populations. This highlights the need for further research on both the efficacy and safety of dextromethorphan-quinidine and other pharmacological interventions for agitation in dementia.

CONCLUSION

This review indicates that there is a scarcity of evidence for the use of dextromethorphan-quinidine for the management of agitation in dementia. There is only one available trial, which demonstrated a decrease in agitation and aggression compared with placebo. However, the trial had a limited number of participants and low representation of patients in nursing home, which further restricts the generalizability of the results. The need to further investigate the effectiveness of different pharmacotherapeutic modalities for the management of agitation in dementia is, therefore, essential.

Table 2 Quality of included studies

Ref.	Randomization	Similar groups initially?	Equal treatment?	Analyzed groups in which they were randomized	Objective/ "blind" treatments?	Overall quality of study
Cummings *et al*[8], 2015	Yes	Yes	Yes	Yes	Yes	Good

Table 3 Results summary from included studies

Ref.	Outcomes	Tolerability	Limitations
Cummings *et al*[8], 2015	In stage 1, mean NPI Agitation/Aggression scores were reduced from 7.1 to 3.8 with dextromethorphan-quinidine and from 7.0 to 5.3 with placebo, $P < 0.001$. In stage 2, mean NPI Agitation/Aggression scores were reduced from 5.8 to 3.8 with dextromethorphan-quinidine and from 6.7 to 5.8 with placebo, $P = 0.02$. The prespecified comparison of NPI Agitation/Aggression scores between patients who were randomized to receive only dextromethorphan-quinidine *vs* only placebo for the entire 10 weeks of the trial also favored dextromethorphan-quinidine over placebo, $P = 0.003$. Response to dextromethorphan-quinidine compared with placebo did not appear to differ by disease stage. The additional prespecified analysis that included both placebo responders and non-responders who were rerandomized in stage 2 did not alter the significance or magnitude of effect of the primary analysis. Sequential parallel comparison design analysis of prespecified secondary outcomes showed significant improvement favoring dextromethorphan-quinidine on global rating scores. Results for changes in the quality of life–Alzheimer disease score, ADCS activities of daily living Inventory, MMSE, and ADAS-Cog were not significant *vs* placebo. Post hoc analyses showed similar improvement in NPI Agitation/Aggression scores with dextromethorphan-quinidine in patients taking concomitant acetylcholinesterase inhibitors, memantine, antidepressants, or antipsychotics n when compared with those not receiving these agents. Lorazepam rescue medication was used by 6.6% of patients in the dextromethorphan-quinidine group during treatment and by 10.4% during treatment with placebo	Treatment-emergent adverse events were reported by 61.2% of patients in the dextromethorphan -quinidine group and 43.3% with placebo group. The most commonly occurring treatment-emergent adverse events were falls (8.6% *vs* 3.9%), diarrhea (5.9% *vs* 3.1%), urinary tract infection (5.3% *vs* 3.9%), and dizziness (4.6% *vs* 2.4%). Serious adverse events occurred in 7.9% patients receiving dextromethorphan-quinidine and in 4.7% of patients receiving placebo. Serious adverse events in patients receiving dextromethorphan-quinidine included chest pain ($n = 2$), anemia, acute myocardial infarction, bradycardia, kidney infection, femur fracture, dehydration, colon cancer, cerebrovascular accident, aggression, and hematuria. Serious adverse events in patients receiving placebo included idiopathic thrombocytopenic purpura, vertigo, pneumonia, gastroenteritis, contusion, transient ischemic attack, and agitation. Eight patients (5.3%) receiving dextromethorphan-quinidine and 4 (3.1%) receiving placebo discontinued treatment owing to adverse events. No deaths occurred during the study. No clinically meaningful between-group differences in electrocardiographic findings were observed	The duration was limited to 10 wk. The dose-escalation schedule limited evaluation of dose-response relationships. Exclusion of concomitant drugs related to quinidine and specific electrocardiographic/cardiac parameters that restricted patient enrollment, may limit the generalizability of study findings. Treatment at experienced trial sites by specialized clinicians under a clinical protocol prescribing frequent assessments may not reflect general practice. The patient sample consisted predominantly of outpatients; agitation in nursing home residents was underrepresented

NPI: Neuropsychiatric inventory; ADCS: Alzheimer's disease cooperative study; MMSE: Mini mental state examination; ADAS-Cog: Alzheimer disease assessment scale–cognitive subscale.

REFERENCES

1 **Bharucha AJ**, Rosen J, Mulsant BH, Pollock BG. Assessment of behavioral and psychological symptoms of dementia. *CNS Spectr* 2002; **7**: 797-802 [PMID: 12947242 DOI: 10.1017/S1092852900024317]

2 **Lyketsos CG**, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 2000; **157**: 708-714 [PMID: 10784462 DOI: 10.1176/appi.ajp.157.5.708]

3 **Zhao QF**, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Xu W, Li JQ, Wang J, Lai TJ, Yu JT. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord* 2016; **190**: 264-271 [PMID: 26540080 DOI: 10.1016/j.jad.2015.09.069]

4 **Salzman C**, Jeste DV, Meyer RE, Cohen-Mansfield J, Cummings J, Grossberg GT, Jarvik L, Kraemer HC, Lebowitz BD, Maslow K, Pollock BG, Raskind M, Schultz SK, Wang P, Zito JM, Zubenko GS. Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. *J Clin Psychiatry* 2008; **69**: 889-898 [PMID: 18494535 DOI: 10.4088/JCP.v69n0602]

5 **Mittal V**, Kurup L, Williamson D, Muralee S, Tampi RR. Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. *Am J Alzheimers Dis Other Demen* 2011; **26**: 10-28 [PMID: 21282274 DOI: 10.1177/1533317510390351]

6 **Taylor CP**, Traynelis SF, Siffert J, Pope LE, Matsumoto RR. Pharmacology of dextromethorphan: Relevance to dextromethorphan/quinidine (Nuedexta®) clinical use. *Pharmacol Ther* 2016; **164**: 170-182 [PMID: 27139517 DOI: 10.1016/j.pharmthera.2016.04.010]

7 **Pioro EP**, Brooks BR, Cummings J, Schiffer R, Thisted RA, Wynn D, Hepner A, Kaye R; Safety, Tolerability, and Efficacy Results Trial of AVP-923 in PBA Investigators. Dextromethorphan plus ultr alow-dose quinidine reduces pseudobulbar affect. *Ann Neurol* 2010; **68**: 693-702 [PMID: 20839238 DOI: 10.1002/ana.22093]

8 **Cummings JL**, Lyketsos CG, Peskind ER, Porsteinsson AP, Mintzer JE, Scharre DW, De La Gandara JE, Agronin M, Davis CS, Nguyen U, Shin P, Tariot PN, Siffert J. Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia: A Randomized Clinical Trial. *JAMA* 2015; **314**: 1242-1254 [PMID: 26393847 DOI: 10.1001/jama.2015.10214]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk:https://www.f6publishing.com/helpdesk
https://www.wjgnet.com