

Pharmacotherapeutic Management of Pseudobulbar Affect

Jack J. Chen, PharmD, BCPS, BCGP

As described in Part 1, patients with pseudobulbar affect (PBA) experience episodes of involuntary and uncontrollable crying and/or laughing outside of socially appropriate circumstances.¹ PBA has also been referred to as emotionalism, emotional lability, or pathological crying and laughing, particularly when attributed to stroke or traumatic brain injury (TBI).^{2,3} Although PBA has been recognized in science and medicine for more than 100 years, it remains an underrecognized and undertreated condition that can be effectively treated with pharmacological methods.⁴ The prevalence of PBA in the general US population is estimated to range from 0.5 to 2 million people.⁵ In a survey study to assess PBA prevalence, more than 900 respondents screened positive for PBA using a validated tool and reported sudden episodes of crying and/or laughter; however, as an indicator of the underrecognition of PBA, none of those respondents reported a specific diagnosis of PBA or related terminology.⁵

The pathophysiology of PBA has helped guide therapeutic treatments. Current prevailing theories suggest that PBA occurs when neural pathways that modulate emotional responses in the brain are interrupted, particularly “descending pathways from the brain (such as the frontal lobes) to the cerebellum through the basis pontis.”⁶ Medical disorders or conditions, such as Parkinson disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), TBI, and stroke, which result in a disruption of those pathways, can produce the hallmark symptoms of PBA—involuntary and uncontrollable laughter and/or crying.^{4,7} The primary neurotransmitters involved in PBA are serotonin and glutamate, and pharmacologic treatments have focused on drugs that modulate these neurotransmitters.^{1,8,9}

Managing PBA

Overview of Off-Label Therapies

Until 2010, there had been no FDA-approved drug with an indication for PBA. Clinicians had consistently used several classes of drugs in an off-label manner to treat it. Drugs in these classes are used to treat various central nervous system (CNS) conditions and target serotonin, glutamate, or dopamine receptors.⁸ As is common with

ABSTRACT

This activity will update pharmacists and other healthcare professionals on current treatments for pseudobulbar affect (PBA). Points of discussion will focus on the off-label therapies traditionally used to treat PBA, the FDA-approved combination drug product with PBA as an indication, and managed care aspects of treating PBA.

Am J Manag Care. 2017;23:S345-S350

For author information and disclosures, see end of text.

TABLE 1. Dose Ranges Used in Treatment of Pseudobulbar Affect^{3,8,18}

Drug	Common Dose Ranges
Off-label treatments	
Tricyclic antidepressants	
Amitriptyline	10-75 mg/day
Imipramine	10-20 mg/day
Nortriptyline	10-25 mg/day
Selective serotonin reuptake inhibitor	
Citalopram	5-40 mg/day ^a
Escitalopram	5-20 mg/day
Fluoxetine	20 mg/day
Sertraline	50-100 mg/day
Other drugs	
Amantadine	5-200 mg 2 times a day
Carbidopa/levodopa	10/100 mg 2 times a day, up to 25/250 mg 4 times a day
Lamotrigine	100 mg/day
Mirtazapine	15-45 mg/day
Reboxetine	2-6 mg 2 times a day
Venlafaxine	37.5 mg 2 times a day
FDA-approved treatment	
Dextromethorphan/quinidine	20/10 mg/daily for 7 days, then increase to 20/10 mg every 12 hours as a maintenance dose

^aThe maximum recommended dose of citalopram is 20 mg/day for patients older than 60 years.

off-label drug use, case studies and small-scale clinical studies provide support for such use in PBA.¹⁰

Tricyclic Antidepressants

Classic tricyclic antidepressants (TCAs) are commonly used to treat PBA. The TCAs have actions as alpha-1 adrenoceptor antagonists, histamine H₁ receptor antagonists, muscarinic receptor antagonists, noradrenaline reuptake inhibitors, 5-HT reuptake inhibitors, and 5-HT_{2A} receptor antagonists, with varying affinities.¹¹ As a qualitative indicator that PBA is distinct from depression, patient responses to TCAs typically occur at lower TCA doses than those used for depression.^{8,10} The time to observable alleviation of PBA symptoms may also be shorter compared with alleviation of depressive symptoms by TCAs.¹² With limited placebo-controlled trials of TCAs for the treatment of PBA and lower doses typically used,¹ the comparative efficacy of TCAs is unclear. Although the lower doses could mitigate risks,¹³ the well-known adverse effects (AEs) of TCAs may limit their use in the treatment of PBA. Anticholinergic effects include

blurred vision, constipation, dry mouth, memory impairment, and urinary retention.¹⁴ Other adverse AEs include sedation and drug–drug interactions (eg, cytochrome P450 2D6 inhibitors can increase levels of TCAs).^{1,11} In addition, the potential cardiac risks of QT prolongation, orthostasis, and tachycardia may also constrain the prescribing of TCAs for PBA.¹⁴⁻¹⁷ For treatment of PBA, the dose ranges of the TCAs commonly used for PBA (eg, amitriptyline, imipramine, and nortriptyline) are listed in **Table 1**.^{3,8,18}

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are also used off label for the treatment of PBA. They block the reuptake of serotonin at neural synapses by selectively inhibiting the 5-HT transporter.¹⁹ As with the TCAs, evidence of SSRI effectiveness in the treatment of PBA is mostly limited to case studies and small-scale clinical studies.¹ The relative efficacies of SSRIs, therefore, are also not entirely clear regarding the treatment of PBA. The dose ranges of the SSRIs commonly used off label for PBA (eg, citalopram, escitalopram, and sertraline) are listed in **Table 1**.^{3,8,18} When using SSRIs, common AEs include dry mouth, headache, insomnia, and sexual function effects such as difficulty with ejaculation or orgasm, vaginal lubrication difficulties, and erectile dysfunction.²⁰ Due to their specific actions on serotonin, potential drug interactions for serotonin syndrome must be kept in mind.^{20,21}

Other Centrally Acting Agents

Other drugs have been used for PBA, primarily in case studies and limited clinical studies. These drugs include other antidepressants (eg, mirtazapine, reboxetine, venlafaxine), lamotrigine, carbidopa/levodopa, and amantadine (based on its effect as a noncompetitive inhibitor of the N-methyl-D-aspartate [NMDA]-sensitive ionotropic glutamate receptor).^{3,8}

Off-label prescribing of prescription drugs is a legitimate medical practice that is typically reserved for cases in which there is no FDA-approved therapy for a particular condition or when approved therapies are ineffective, not tolerated, or contraindicated for a particular patient.²²⁻²⁴ Prescribers and pharmacists should ensure that there is proper patient education and consent for off-label use.²⁴ For any of the off-label uses of drugs for PBA, the recommended and clinically prudent approach is to start with a low dose and gradually titrate to achieve the desired therapeutic benefit.^{1,8}

Overview of FDA-Approved Therapy: Dextromethorphan and Quinidine

Currently, the only FDA-approved drug for the treatment of PBA is a capsule formulation that combines dextromethorphan hydrobromide (20 mg) and quinidine sulfate (10 mg). The initial dose is 1 capsule daily for 7 days, with an increase to 1 capsule every 12 hours as a maintenance dose.¹⁸ First approved by the FDA in October 2010,²⁵

dextromethorphan/quinidine has an indication for the treatment of PBA without specification of the underlying cause.¹⁸

Pharmacology and Mechanism of Action

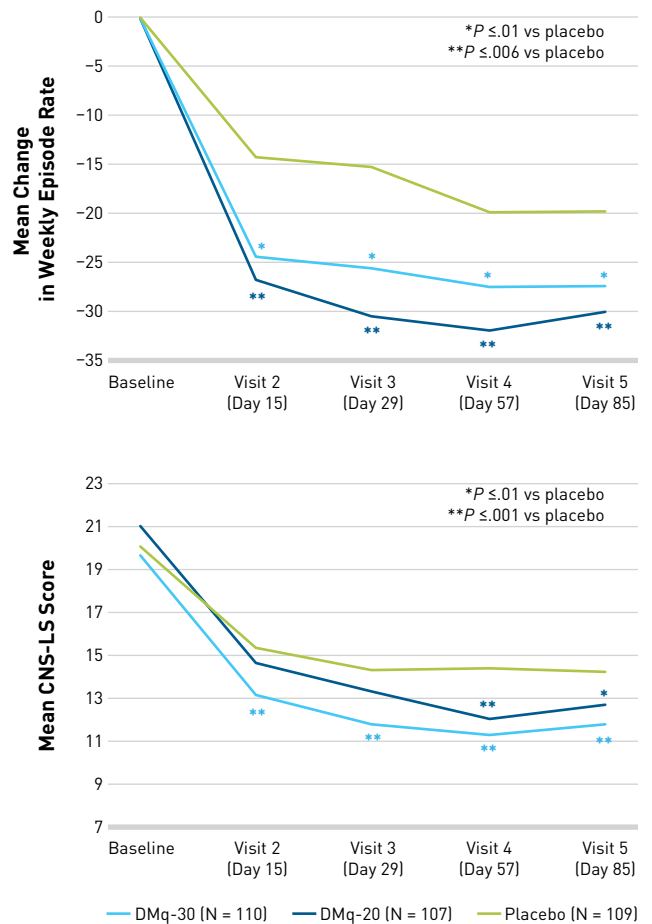
Dextromethorphan, which is most commonly used as an antitussive in cough and cold remedies, has CNS activity both as an uncompetitive antagonist of the NMDA-sensitive ionotropic glutamate receptor and as a sigma-1 receptor agonist.²⁶⁻²⁸ These actions align with the prevailing theories on the pathophysiology of PBA.^{1,6,8,9} Preliminary reports that suggested the efficacy of dextromethorphan for PBA prompted additional research on its use for treating the condition.^{29,30}

For dextromethorphan to exert its intended effect, the drug must reach the neural targets in the CNS. The physiochemical properties of dextromethorphan, however, limit its uptake. When administered orally, dextromethorphan is rapidly metabolized by the cytochrome P450 2D6 isoform (CYP2D6) to dextrorphan, which is subsequently glucuronidated, resulting in very low bioavailability of dextromethorphan.³¹⁻³⁴ Dextrorphan has antitussive effects, and it is believed to be the compound responsible for psychoactive properties based on higher affinity for the NMDA receptor.^{35,36} To increase the oral bioavailability of dextromethorphan, one successful approach is to inhibit CYP2D6 metabolism via the coadministration of the CYP2D6 inhibitor, quinidine.^{33,37} Clinical studies focusing on modulating the metabolism of dextromethorphan by coadministration of quinidine supported the rationale for this approach, and the relatively low-dose combination of dextromethorphan and quinidine became the basis for the commercial product approved for PBA.^{18,34,38}

Clinical Efficacy

Double-blind clinical studies provide supporting data on the efficacy of dextromethorphan/quinidine in the treatment of PBA. Brooks et al studied the drug combination at a dose of 30 mg each of dextromethorphan and quinidine (dosed twice daily) in patients with ALS, with comparator groups of each drug alone.³⁹ Subjects who received the drugs in combination demonstrated significantly greater improvements in the Center for Neurologic Study-Lability Scale (CNS-LS) scores by 3.3 points compared with dextromethorphan alone and by 3.7 points compared with quinidine alone for up to 28 days.³⁹ Improvements in quality of life (QOL) and quality of relationship scales were also observed in the drug combination group compared with each individual drug.³⁹ In a study of patients with MS, the combination (30 mg of each dosed twice daily) was compared with placebo over the course of 85 days.⁴⁰ Similar to the study in patients with ALS, the combination group demonstrated statistically significant greater reductions in CNS-LS scores compared with placebo, as well as statistically significant improvements in the number of laughing or crying episodes, QOL, quality of relationships, and pain intensity measures.⁴⁰

FIGURE. 12-Week Time Course of Pseudobulbar Affect Weekly Episode Rate and Center for Neurologic Study-Lability Scale Score (intent-to-treat population)^{29,a}



CNS-LS indicates Center for Neurologic Study-Lability Scale; DMq-30, dextromethorphan combined with ultra-low-dose quinidine at 30/10 mg; DMq-20, dextromethorphan combined with ultra-low-dose quinidine at 20/10 mg. ^aWeekly rates (top chart) are shown as change from baseline at each visit in mean daily rates. CNS-LS scores (bottom chart) are the means at each visit. Reprinted with permission from Piro EP, Brooks BR, Cummings J, et al; Safety, Tolerability, and Efficacy Results Trial of AVP-923 in PBA Investigators. *Ann Neurol.* 2010;68(5):693-702. doi: 10.1002/ana.22093.

FDA approval of dextromethorphan/quinidine was granted on the basis of a large controlled trial in 326 patients with MS or ALS who had clinically significant PBA. Patients were randomized to either placebo or 2 doses of dextromethorphan/quinidine, 30/10 mg or 20/10 mg, dosed twice daily. All study groups, including the placebo group, demonstrated lower daily episode rates of PBA and lower CNS-LS scores compared with baseline (Figure²⁹). Of the 283 patients who completed the trial, patients receiving the drug combination at either dose had lower daily episode rates of PBA compared with placebo; 46.9% and 49.0% lower rates in those treated with the 30/10-mg dose and 20/10-mg dose, respectively. Patients receiving the drug combination achieved greater reductions

in CNS-LS scores (–8.2 points for the 30/10-mg group; –8.2 points for the 20/10-mg group; –5.7 points for the placebo group).²⁹

It is notable that the American Academy of Neurology (AAN) practice parameter update on the care of patients with ALS made a recommendation for use of dextromethorphan/quinidine before its FDA approval. The AAN recommended that if approved by the FDA, and the AEs were acceptable, dextromethorphan/quinidine should be considered for symptoms of pseudobulbar affect in patients with ALS as a Level B recommendation.⁴¹ In addition, the AAN 2014 guidelines on the assessment and management of psychiatric disorders in individuals with MS recommended that dextromethorphan/quinidine is possibly effective and safe and may be considered for treating individuals with MS with PBA (Level C, 1 Class 2 study).⁴²

Common AEs and Precautions

Dextromethorphan/quinidine is likely to be administered to patients for extended periods of time in chronic and progressive neurological diseases, such as AD, MS, and PD, and it is essential that a long-term safety profile is favorable. In a trial by Pioro et al, the 20/10-mg and 30/10-mg dextromethorphan/quinidine treatment groups were well tolerated, with low discontinuation rates. Among the most frequently reported AEs, falls, dizziness, and diarrhea occurred at a higher rate in the dextromethorphan/quinidine groups compared with placebo.²⁹ Urinary tract infection was also reported at a higher frequency in the dextromethorphan/quinidine 30/10-mg group compared with placebo.²⁹

Longer-term safety of dextromethorphan/quinidine treatment of PBA was investigated in an open-label, 52-week, multicenter study.⁴³ A total of 553 patients were recruited (40.3% had MS; 31.8%, ALS; 8.3%, stroke; 3.8%, TBI) and were treated with dextromethorphan/quinidine 30/30 mg twice daily.⁴³ The most frequent AEs during treatment were nausea (24.8%), headache (22.8%), dizziness (19.5%), falls (16.5%), diarrhea (16.3%), fatigue (14.6%), and weakness (13.7%).⁴³ These long-term AEs are consistent with results observed in placebo-controlled trials.

As dextromethorphan is a substrate for CYP2D6 and quinidine is an inhibitor of CYP2D6 and p-glycoprotein, there is the potential for drug interactions.⁴⁴ Dose reductions of desipramine, paroxetine, and digoxin are advised when administering the dextromethorphan/quinidine product. Exposure to these drugs can increase substantially when coadministered with dextromethorphan/quinidine. The exposure of desipramine can increase 8-fold and the digoxin and paroxetine exposure, up to 2-fold.¹⁸

Dextromethorphan has the potential of inducing serotonin syndrome, a potentially fatal syndrome manifested by high levels of the neurotransmitter, serotonin.^{21,45} Combined with quinidine, which inhibits dextromethorphan metabolism, the risk of serotonin syndrome should be considered. For this reason, patients taking dextromethorphan/quinidine must not take monoamine oxidase

inhibitors for 14 days before and after dextromethorphan/quinidine therapy.¹⁸ Quinidine, known for QT interval prolongation, is also metabolized by CYP3A4, and these factors should be considered in patients who are taking CYP3A4-inhibiting drugs and drugs that can also prolong the QT interval.^{46,47}

Role of the Pharmacist in Monitoring Patients With PBA

Educate Patients and Caregivers About PBA and Available Treatments

Because studies on the impact of pharmacist interventions in PBA have not yet been published, standard pharmacist patient care processes and clinical judgment best serve patients. As an underrecognized condition, educating patients and their caregivers about PBA may help improve perceptions regarding the stigma of the condition and minimize social withdrawal. If patients have not already been screened for PBA, pharmacists may suggest the use of the Pathological Laughter and Crying Scale, an 18-item clinical interview assessment that can be administered by an appropriate healthcare provider.⁴⁸ The CNS-LS tool, a self-administered 7-item questionnaire commonly used in clinical studies of PBA, may also be useful when used in the designated clinical environment.⁴⁹

With therapeutic alternatives that include both approved and off-label treatments, pharmacists can and should be a primary resource of drug information for patients and their caregivers. Pharmacists also have a role in advising prescribers on appropriate off-label uses of drugs.⁵⁰ In situations where patients are unable to swallow whole capsules, pharmacists may also use their expertise to compound liquid formulations of, for example, dextromethorphan and quinidine, as a suspension.⁵¹

Assist Patients/Caregivers With Coping Strategies for Living With PBA

The manifestations of PBA can negatively affect QOL measures in patients and their caregivers.^{52,53} Patients with PBA may be more prone to depression, with a corresponding propensity to take antidepressants at a higher rate compared with cohorts without PBA.⁵⁴ This can have implications in regard to choosing appropriate pharmacotherapy for PBA.

Education is essential to the clinical management of this condition. Patients and family members must be educated about the general nature of PBA, and pharmacists are in a good position to educate patients and family members about expectations for duration of treatment. For example, in TBI or stroke, the need for treatment may diminish as recovery occurs and neurological function is restored. However, in MS, ALS, AD, and PD, treatment is likely to be needed over extended durations due to their progressive and irreversible nature. Teaching that PBA is distinct from depression and other psychiatric disorders can minimize the emotional stress on patients

and family members. Pharmacists can also help patients and family members to identify activities or factors that exacerbate symptoms, such as anxiety or excessive stress. Patients who experience PBA are often adjusting to a major illness such as ALS, MS, stroke, or TBI. Therefore, working within an interprofessional model, pharmacists can reinforce to patients and family members the availability and integration of nonpharmacologic interventions (eg, physical, mental, and spiritual practices) in daily life after diagnosis with these disorders.

Managed Care Considerations in PBA

Two of the primary considerations in managed care’s evaluation of pharmacotherapy are cost and efficacy. The current retail cost of the commercial combination product is approximately \$800 for 60 capsules, which correlates to a 30-day supply at the recommended maintenance dose of 1 capsule twice daily.⁵⁵ Therefore, at maintenance doses, the approximate cost translates to \$9600 per year. The cost to patients is affected by factors including insurance coverage and possible financial assistance from the manufacturer. The cost of pharmacotherapy, however, is not the only cost to be considered.

The potential savings in overall healthcare costs should also be considered in the managed care and other settings. In an analysis of veterans with TBI, Rudolph et al found that total healthcare costs rose with increasing severity of PBA symptoms.⁵⁶ Patients with CNS-LS scores <13 had average (± standard deviation) total healthcare costs of \$2825 (±\$5172). When patient CNS-LS scores were between 13 and 20, the average total healthcare costs rose by approximately \$900 to \$3721 (±\$6826). For patients with CNS-LS scores ≥21, average total healthcare costs were \$5718 (±\$7233), an increase of almost \$3000 from patients with scores <13.⁵⁶ One of the confounding factors in the study was the absence or presence of posttraumatic stress disorder (PTSD). Patients diagnosed with PTSD had substantially greater healthcare costs at all CNS-LS score levels compared with patients without PTSD.⁵⁶ Although limited in scope and size and wide standard deviations, this study’s results suggest that managing PBA may decrease overall healthcare costs and that further study is warranted to answer the question.

While the efficacy of the commercial combination product has passed the scrutiny of the FDA, some clinicians have expressed concern about the lack of direct comparison studies with other potentially less expensive therapies that have been used for PBA; that is, the off-label use of TCAs, SSRIs, and other products, as well as the overall impact of drug marketing on healthcare costs.⁵⁷⁻⁵⁹ Similar to other studies cited here, this study included manufacturer support and employee co-authorship. The absence of studies that are clear of manufacturer support may be similar to other therapeutic

TABLE 2. Additional Resources

Resources	Link to Resources
Pseudobulbar Affect Info	
Website created and hosted by Avanir Pharmaceuticals, Inc.	pbainfo.org/
National Stroke Association	stroke.org/ stroke.org/stroke-resources/resource-library/ pseudobulbar-affect-emotional-mismatch
Brain Injury Association of America	stroke.org/sites/default/files/resources/ PBA%20Infographic_0.pdf biausa.org/

areas. The acknowledgment of industry support and involvement in the published studies address some concerns of transparency and potential effects of industry support that can assist clinicians in making informed decisions.^{60,61} In the case of PBA, clinicians and managed care professionals can base such decisions on the limited number of clinical trials of off-label–use drugs and/or on the larger, manufacturer-sponsored clinical trials, as well as their overall clinical knowledge.

Conclusion

PBA is an underrecognized and undertreated condition that affects upwards of 2 million individuals in the United States. Treatment options include the off-label use of centrally acting drugs, such as antidepressants, and the FDA-approved drug combination of dextromethorphan and quinidine. Additional resources can be found in **Table 2**. With appropriate education, pharmacists can play an important role in the education, assessment, and monitoring of pharmacologic treatments for PBA that can potentially result in better outcomes. They can collaborate with patients, caregivers, and other healthcare professionals in the management of PBA. ■

Author affiliation: Loma Linda University, Loma Linda, CA; Marshall B. Ketchum University, Fullerton, CA.

Funding source: This activity is supported by an independent educational grant from Avanir Pharmaceuticals, Inc.

Author disclosures: Dr Chen has reported that he has no relevant financial relationships with commercial interests to disclose.

Authorship information: Analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and supervision.

Address correspondence to: jchen@ketchum.edu.

REFERENCES

1. Miller A, Pratt H, Schiffer RB. Pseudobulbar affect: the spectrum of clinical presentations, etiologies and treatments. *Expert Rev Neurother*. 2011;11(7):1077-1088. doi: 10.1586/ern.11.68.
2. Hackett ML, Yang M, Anderson CS, Horrocks JA, House A. Pharmaceutical interventions for emotionalism after stroke. Hackett ML, ed. *Cochrane Database Syst Rev*. 2010;(2):CD003690. doi: 10.1002/14651858.CD003690.pub3.
3. Balakrishnan P, Rosen H. The causes and treatment of pseudobulbar affect in ischemic stroke. *Curr Treat Options Cardiovasc Med*. 2008;10(3):216-222.
4. Sauvé WM. Recognizing and treating pseudobulbar affect. *CNS Spectr*. 2016;21(S1):34-44. doi: 10.1017/S1092852916000791.

5. Work SS, Colamonic JA, Bradley WG, Kaye RE. Pseudobulbar affect: an under-recognized and under-treated neurological disorder. *Adv Ther*. 2011;28(7):586-601. doi: 10.1007/s12325-011-0031-3.
6. Parvizi J, Coburn KL, Shilcutt SD, Coffey CE, Lauterbach EC, Mendez MF. Neuroanatomy of pathological laughing and crying: a report of the American Neuropsychiatric Association Committee on Research. *J Neuropsychiatry Clin Neurosci*. 2009;21(1):75-87. doi: 10.1176/jnp.2009.21.1.75.
7. Lapchak PA. Neuronal dysregulation in stroke-associated pseudobulbar affect (PBA): diagnostic scales and current treatment options. *J Neural Neurophysiol*. 2015;6(5):323. doi: 10.4172/2155-9562.1000323.
8. Wortzel HS, Oster TJ, Anderson CA, Arciniegas DB. Pathological laughing and crying: epidemiology, pathophysiology and treatment. *CNS Drugs*. 2008;22(7):531-545.
9. Ahmed A, Simmons Z. Pseudobulbar affect: prevalence and management. *Ther Clin Risk Manag*. 2013;9:483-489. doi: 10.2147/TCRM.S53906.
10. Rosen H. Dextromethorphan/quinidine sulfate for pseudobulbar affect. *Drugs Today (Barc)*. 2008;44(9):661-668. doi: 10.1358/dot.2008.44.9.1258664.
11. Gitlman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol*. 2007;151(6):737-748. doi: 10.1038/sj.bjp.0707253.
12. Arciniegas DB, Lauterbach EC, Anderson KE, et al. The differential diagnosis of pseudobulbar affect (PBA). Distinguishing PBA among disorders of mood and affect. Proceedings of a roundtable meeting. *CNS Spectr*. 2005;10(5):1-14.
13. Furukawa TA, McGuire H, Barbuti C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. *BMJ*. 2002;325(7371):991. doi: 10.1136/bmj.325.7371.991.
14. Trindade E, Menon D, Topfer L-A, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *Can Med Assoc J*. 1998;159(10):1245-1252.
15. Pachter P, Kecskemeti V. Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? *Curr Pharm Des*. 2004;10(20):2463-2475. doi: 10.2174/1381612043383872.
16. Blackwell B. Adverse effects of antidepressant drugs. Part 1: monoamine oxidase inhibitors and tricyclics. *Drugs*. 1981;21(3):201-219. doi: 10.2165/00003495-198121030-00002.
17. Glassman AH. Cardiovascular effects of tricyclic antidepressants. *Annu Rev Med*. 1984;35(1):503-511. doi: 10.1146/annurev.me.35.020184.002443.
18. Nuedexta [package insert]. Aliso Viejo, CA: Avian Pharmaceuticals, Inc; 2015. nuedexta.com/sites/default/files/pdfs/Prescribing_Information.pdf. Accessed September 27, 2017.
19. Goodnick PJ, Goldstein BJ. Selective serotonin reuptake inhibitors in affective disorders — I. Basic pharmacology. *J Psychopharmacol*. 1998;12(suppl 4):S5-S20. doi: 10.1177/0269881198012003021.
20. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Prim Care Companion J Clin Psychiatry*. 2001;3(1):22-27.
21. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112-1120. doi: 10.1056/NEJMr041867.
22. Walton SM, Schumock GT, Lee K-V, Alexander GC, Meltzer D, Stafford RS. Prioritizing future research on off-label prescribing: results of a quantitative evaluation. *Pharmacotherapy*. 2008;28(12):1443-1452. doi: 10.1592/phco.28.12.1443.
23. Largent EA, Miller FG, Pearson SD. Going off-label without venturing off-course. *Arch Intern Med*. 2009;169(17):1745-1747. doi: 10.1001/archinternmed.2009.314.
24. Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med J Aust*. 2006;185(10):544-548.
25. Nuedexta (dextromethorphan hydrobromide; quinidine sulfate) capsules. US Food and Drug Administration website. accessdata.fda.gov/drugsatfda_docs/applletter/2010/021879s000ltr.pdf. Published October 29, 2010. Accessed September 29, 2017.
26. Tortella FC, Pellicano M, Bowery NG. Dextromethorphan and neuromodulation: old drug coughs up new activities. *Trends Pharmacol Sci*. 1989;10(12):501-507.
27. Parsons CG, Gruner R, Rozental J, Millar J, Lodge D. Patch clamp studies on the kinetics and selectivity of N-methyl-D-aspartate receptor antagonism by memantine (1-amino-3,5-dimethyladamantan). *Neuropharmacology*. 1993;32(12):1337-1350.
28. Musacchio JM, Klein M, Paturzo JJ. Effects of dextromethorphan site ligands and allosteric modifiers on the binding of (+)-[3H]-(-)-3-hydroxyphenyl-N-(1-propyl)piperidine. *Mol Pharmacol*. 1989;35(1):1-5.
29. Piore EP, Brooks BR, Cummings J, et al; Safety, Tolerability, and Efficacy Results Trial of AVP-923 in PBA Investigators. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol*. 2010;68(5):693-702. doi: 10.1002/ana.22093.
30. Dubovsky SL. Dextromethorphan/quinidine for pseudobulbar affect. *Clin Investig (Land)*. 2014;4(6):549-554.
31. Schmid B, Bircher J, Preisig R, Kupfer A. Polymorphic dextromethorphan metabolism: co-segregation of oxidative O-demethylation with debrisoquin hydroxylation. *Clin Pharmacol Ther*. 1985;38(6):618-624.
32. Duché JC, Quérol-Ferrer V, Barré J, Mésangeau M, Tillement JP. Dextromethorphan O-demethylation and dextromethorphan glucuronidation in a French population. *Int J Clin Pharmacol Ther Toxicol*. 1993;31(8):392-398.
33. Zhang Y, Britto MR, Valderhaug KL, Wedlund PJ, Smith RA. Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. *Clin Pharmacol Ther*. 1992;51(6):647-655.
34. Pope LE, Khalil MH, Berg JE, Stiles M, Yakatan GJ, Sellers EM. Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol*. 2004;44(10):1132-1142. doi: 10.1177/0091270004269521.
35. Dicpinigaitis PV, Morice AH, Birring SS, et al. Antitussive drugs—past, present, and future. *Pharmacol Rev*. 2014;66(2):468-512. doi: 10.1124/pr.111.005116.
36. Reissig CJ, Carter LP, Johnson MW, Mintzer MZ, Klinedinst MA, Griffiths RR. High doses of dextromethorphan, an NMDA antagonist, produce effects similar to classic hallucinogens. *Psychopharmacology (Berl)*. 2012;223(1):1-15. doi: 10.1007/s00213-012-2680-6.
37. Schadel M, Wu D, Otton SV, Kalow W, Sellers EM. Pharmacokinetics of dextromethorphan and metabolites in humans: influence of the CYP2D6 phenotype and quinidine inhibition. *J Clin Psychopharmacol*. 1995;15(4):263-269.
38. Capon DA, Bochner F, Kerry N, Mikus G, Danz C, Somogyi AA. The influence of CYP2D6 polymorphism and quinidine on the disposition and antitussive effect of dextromethorphan in humans. *Clin Pharmacol Ther*. 1996;60(3):295-307. doi: 10.1016/S0009-9236(96)90056-9.
39. Brooks BR, Thisted RA, Appel SH, et al; AVP-923 ALS Study Group. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. *Neurology*. 2004;63(8):1364-1370.
40. Panitch HS, Thisted RA, Smith RA, et al; Pseudobulbar Affect in Multiple Sclerosis Study Group. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Ann Neurol*. 2006;59(5):780-787. doi: 10.1002/ana.20828.
41. Miller RG, Jackson CE, Kasarskis EJ, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2009;73(15):1227-1233. doi: 10.1212/WNL.0b013e3181b0c1a4.
42. Minden SL, Feinstein A, Kalb RC, et al; Guideline Development Subcommittee of the American Academy of Neurology. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82(2):174-181. doi: 10.1212/WNL.0000000000000013.
43. Pattee GL, Wymer JP, Lomen-Hoerth C, Appel SH, Formella AE, Pope LE. An open-label multicenter study to assess the safety of dextromethorphan/quinidine in patients with pseudobulbar affect associated with a range of underlying neurological conditions. *Curr Med Res Opin*. 2014;30(11):2255-2265. doi: 10.1185/03007995.2014.940040.
44. Schoedel KA, Morrow SA, Sellers EM. Evaluating the safety and efficacy of dextromethorphan/quinidine in the treatment of pseudobulbar affect. *Neuropsychiatr Dis Treat*. 2014;10:1161-1174. doi: 10.2147/NDT.S30713.
45. Schwartz AR, Pizon AF, Brooks DE. Dextromethorphan-induced serotonin syndrome. *Clin Toxicol*. 2008;46(8):771-773.
46. Roden DM, Thompson KA, Hoffman BF, Woosley RL. Clinical features and basic mechanisms of quinidine-induced arrhythmias. *J Am Coll Cardiol*. 1986;8(1, suppl A):73A-78A.
47. Damkier P, Hansen LL, Brosen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol*. 1999;48(6):829-838.
48. Robinson RG, Parikh RM, Lipsley JR, Starkstein SE, Price TR. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. *Am J Psychiatry*. 1993;150(2):286-293. doi: 10.1176/ajp.150.2.286.
49. Moore SR, Gresham LS, Bromberg MB, Kasarkis EJ, Smith RA. A self report measure of affective lability. *J Neurol Neurosurg Psychiatry*. 1997;63(1):89-93. doi: 10.1136/JNPP.63.1.89.
50. Basak R, Bentley JP, McCaffrey DJ, Bouldin AS, Banahan BF. The role of perceived impact on relationship quality in pharmacists' willingness to influence indication-based off-label prescribing decisions. *Soc Sci Med*. 2015;132:181-189. doi: 10.1016/j.socscimed.2015.03.028.
51. Wahler RG, Reiman AT, Schrader JV. Use of compounded dextromethorphan-quinidine suspension for pseudobulbar affect in hospice patients. *J Palliat Med*. 2017;20(3):294-297. doi: 10.1089/jpm.2016.0277.
52. Colamonic J, Formella A, Bradley W. Pseudobulbar affect: burden of illness in the USA. *Adv Ther*. 2012;29(9):775-798. doi: 10.1007/s12325-012-0043-7.
53. Brooks BR, Crumacker D, Fellus J, Kantor D, Kaye RE. PRISM: a novel research tool to assess the prevalence of pseudobulbar affect symptoms across neurological conditions. Zhang XY, ed. *PLoS One*. 2013;8(8):e72232. doi: 10.1371/journal.pone.0072232.
54. Strowd RE, Cartwright MS, Okun MS, Haq I, Siddiqui MS. Pseudobulbar affect: prevalence and quality of life impact in movement disorders. *J Neurol*. 2010;257(8):1382-1387. doi: 10.1007/s00415-010-5550-3.
55. Nuedexta prices, coupons and patient assistance programs. Drugs.com website. drugs.com/price-guide/nuedexta. Accessed October 2, 2017.
56. Rudolph JL, Fonda JR, Hunt PR, et al. Association of pseudobulbar affect symptoms with quality of life and healthcare costs in veterans with traumatic brain injury. *J Affect Disord*. 2016;190:150-155. doi: 10.1016/j.jad.2015.10.003.
57. Meininger V. Treatment of emotional lability in ALS. *Lancet Neurol*. 2005;4(2):70. doi: 10.1016/S1474-4422(05)00970-1.
58. Pollack A. Marketing a disease, and also a drug to treat it. *The New York Times* website. nytimes.com/2005/05/09/business/health/marketing-a-disease-and-also-a-drug-to-treat-it.html. Published May 9, 2005. Accessed October 2, 2017.
59. Johnston SC, Hauser SL. Marketing and drug costs: Who is laughing and crying? *Ann Neurol*. 2007;61(2):A11-A12. doi: 10.1002/ana.21100.
60. Ross JS, Gross CP, Krumholz HM. Promoting transparency in pharmaceutical industry-sponsored research. *Am J Public Health*. 2012;102(1):72-80. doi: 10.2105/AJPH.2011.300187.
61. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. In: Lundh A, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2017. doi: 10.1002/14651858.MR000033.pub3.