

It is illegal to post this copyrighted PDF on any website.

Development of Insomnia Associated With Different Formulations of Bupropion

Kamal Gandotra, MD^{a,b,c,d,*}; George E. Jaskiw, MD^{b,c}; Scott G. Williams, MD^{e,f}; Matthew A. Fuller, PharmD^{g,h}; Peijun Chen, MD^{b,c}; Brigid Wilson, PhDⁱ; Rawad ElGhoul, MD^d; Eric Konicki, MD^{b,c}; and Kingman Perkins Strohl, MD^{d,j}

Bupropion is a widely prescribed antidepressant with efficacy for major depressive disorder, seasonal affective disorder, smoking tobacco cessation, and attention-deficit/hyperactivity disorder.¹ While bupropion's advantages include a relatively low risk of inducing restless leg syndrome² or rapid eye movement sleep behavioral disorder,³ its alerting effects may disrupt sleep, particularly when a short-acting formulation is administered late in the day.⁴ Awareness of the kinetics and pharmacology of bupropion can mitigate such sleep-disturbing effects while exploiting antidepressant effects. Bupropion is a weak norepinephrine-dopamine reuptake inhibitor that does not show significant antagonism at histaminic or muscarinic receptors and has a low prevalence of sexual side effects.⁵ While bupropion is not a classic stimulant,⁶ its ability to increase dopamine and norepinephrine can result in nonspecific stimulation.⁵ Sleep medicine practitioners and others can now optimize selection of bupropion formulations to minimize the risk of insomnia.

The stimulating effects in wakefulness of bupropion include restlessness, activation, tremors, and nausea and typically coincide with peak (Cmax) plasma concentrations. The original immediate-release (IR) preparation has a half-life requiring 3 dosing times/day. The sustained-release (SR)

(twice/day dosing) and extended-release (XL) (once/day dosing) formulations were developed to improve tolerability and adherence. Given the dosing regimen, patients with IR, SR, and XL formulations are exposed to 3, 2, and 1 instances of Cmax daily, respectively.³ Furthermore, the time to achieve Cmax (Tmax) is shorter for the IR dosage form (2 hours) relative to the SR (3 hours) and XL (5 hours) dosage forms.³ In combination, these characteristics may affect tolerability. A morning dosing of the XL formulation, in particular, results in lower drug levels during evening hours³ and may result in a lower risk of insomnia. We evaluated the effects of a possible association between the different bupropion formulations and treatment-emergent insomnia in veterans with major depressive disorder prescribed bupropion based on provider discretion.

Methods

A retrospective chart review was conducted of outpatients treated at the Veterans Affairs Northeast Ohio Healthcare System, Cleveland, Ohio. Charts were selected of patients who presented over a 3-month period and met the following criteria: (1) referred to mental health clinic for symptoms of major depressive disorder (*DSM-5* criteria), (2) did not have comorbid insomnia (initial Insomnia Severity Index [ISI, see Supplementary Appendix 1]⁷ score < 7 with no subjective sleep complaints), (3) Apnea-Hypopnea Index score < 5/h, (4) were started on any formulation of bupropion (IR, SR, or XL), (5) were not on medications that influence sleep, and (6) did not have a hypersomnolence condition. ISI, Clinically Useful Depression Outcome Scale (CUDOS, see Supplementary Appendix 2),⁸ and Epworth Sleepiness Scale (ESS)⁹ scores were determined at baseline and at 4–6 weeks and 7–12 weeks after initiation of bupropion. Self-reporting timing of doses was extracted from the chart. For ISI and CUDOS scores, linear mixed-effects models were used to assess the interaction of treatment formulation (IR, SR, XL) and time. Analyses were performed in R 3.5.1 using the lme4 and emmeans packages (<https://www.r-project.org/>). A random intercept for each subject was estimated given unbalanced groups and missing observations due to discontinuations. For each of 3 time points, differences across fixed-effect estimates of treatments were determined and Tukey *P* value adjustments imposed (*P* < .05).

Results

A total of 30 veterans (aged 25 to 58 years) met entry criteria. In 2 patients, bupropion was discontinued secondary

^aLouis Stokes VA Medical Center, Cleveland, Ohio

^bPsychiatry Service, Louis Stokes VA Medical Center, Cleveland, Ohio

^cDepartment of Psychiatry, Case Western Reserve University, Cleveland, Ohio

^dDivision of Pulmonary, Critical Care, and Sleep Medicine, Louis Stokes VA Medical Center, Cleveland, Ohio

^eSleep Disorders Center, Department of Medicine, Walter Reed National Military Medical Center, Bethesda, Maryland

^fDepartment of Medicine, Uniformed Services University of the Health Sciences, Bethesda

^gNational PBM Clinical Pharmacy Program Manager VHA Pharmacy Benefits Management Services, Hines, Illinois

^hDepartments of Psychiatry and Psychology, Case Western Reserve University, Cleveland, Ohio

ⁱGeriatric Research Educational and Clinical Center (GRECC), Louis Stokes VA Medical Center, Cleveland, Ohio

^jDivision of Pulmonary, Critical Care and Sleep Medicine, University Hospitals, Case Western Reserve University, Cleveland, Ohio

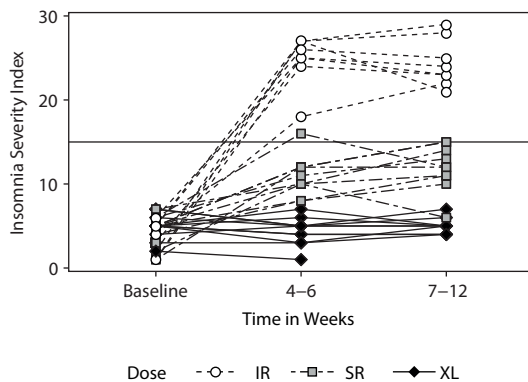
*Corresponding author: Kamal Gandotra, MD, Louis Stokes VAMC, 10701 East Blvd, Cleveland, OH 44106 (Kamal.Gandotra2@va.gov).

Prim Care Companion CNS Disord 2021;23(1):20br02621

To cite: Gandotra K, Jaskiw GE, Williams SG, et al. Development of insomnia associated with different formulations of bupropion. *Prim Care Companion CNS Disord*. 2021;23(1):20br02621.

To share: <https://doi.org/10.4088/PCC.20br02621>

© Copyright 2021 Physicians Postgraduate Press, Inc.

Figure 1. Insomnia Severity Index Results Over Time^a

^aSymbols are connected by lines for each individual, with the connections shown by formulation. The changes for each patient over time (weeks) with different formulations of bupropion are provided. The solid gray horizontal line indicates the generally accepted threshold for moderate insomnia. All ISI values were ≤ 7 at baseline for all groups. Scores < 7 are found in those with no clinically significant sleep complaints.

Abbreviations: IR = immediate release, SR = sustained release, XL = extended release.

to tinnitus or agitation, yielding a final sample of 28 (27 men, 1 woman).

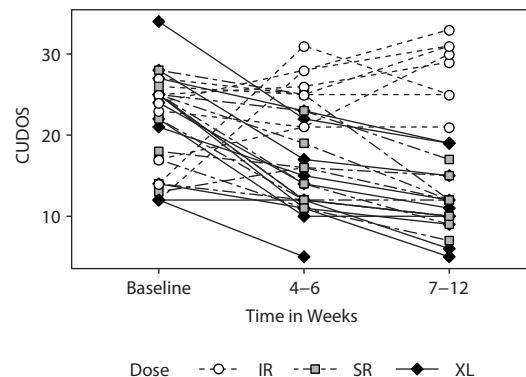
Veterans treated with both SR and IR formulations presented more often with complaints of insomnia based on the ISI compared to patients treated with the XL dosage form. We observed a statistically significant interaction of dose and time ($F = 99.7$, $df = 4$, $P < .01$). The mean post baseline ISI score was significantly lower in patients treated with bupropion XL than in patients treated with bupropion IR or bupropion SR (Figure 1).

A similar model predicting CUDOS scores included a significant interaction of dose and time ($F = 18.9$, $df = 4$, $P < .01$), indicating the IR formulation of bupropion was least effective in lowering the depression score (Figure 2).

For the ESS, there was no difference among groups at baseline. While the ESS scores for the IR formulation were significantly higher than those for the other 2 formulations at other time points, no difference was observed between SR and XL at any time point on the ESS (Figure 3). The ESS values did not change significantly over time during administration of any of the formulations. This finding may be attributed to the pathophysiology of insomnia, as it is considered to be a disorder of arousal. Alternatively, the IR formulation causes medication-induced insomnia, which leads to next-day tiredness as a result of sleeping poorly.

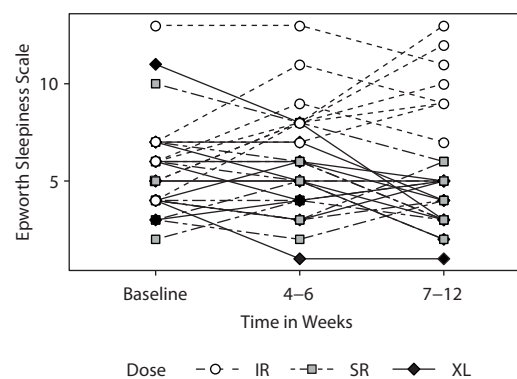
Discussion

Psychotropic drugs can contribute to the pathogenesis and maintenance of insomnia. Activating antidepressants such as bupropion may be especially culpable.⁵ Our chart review found that in outpatients presenting with depression but without comorbid insomnia, high rates of insomnia developed after initiation of treatment with IR formulations of bupropion but not after a single-dose morning

Figure 2. Clinically Useful Depression Outcome Scale (CUDOS) Results Over Time^a

^aSymbols are connected by lines for each individual, with the connections shown by formulation. The changes for each patient over time (weeks) with different formulations of bupropion are provided. Changes in clinical depression outcome scale scores in each patient over 12 weeks with symbols for all 3 formulations of bupropion are shown.

Abbreviations: IR = immediate release, SR = sustained release, XL = extended release.

Figure 3. Epworth Sleepiness Scale Results Over Time^a

^aSymbols are connected by lines for each individual, with the connections shown by formulation. The changes for each patient over time (weeks) with different formulations of bupropion are provided.

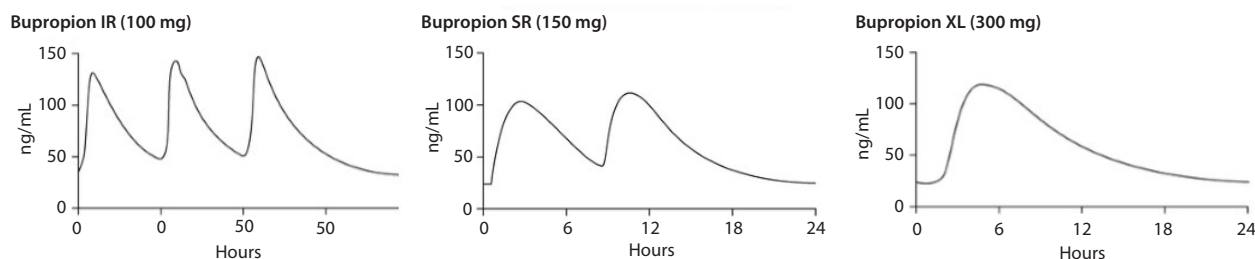
Abbreviations: IR = immediate release, SR = sustained release, XL = extended release.

administration of a slow-release, long-acting formulation (see Figure 1).

These findings underscore the importance of considering potential stimulating effects of bupropion expected to correlate with peak (C_{max}) plasma concentrations. Given the dosing regimens, patients with IR, SR, and XL formulations are exposed to 3, 2, and 1 instances of C_{max} daily. Furthermore, the time to achieve C_{max} (T_{max}) is shorter for IR (2h) relative to SR (3h) and XL (5h) formulations³ (see Figure 3). In combination, these characteristics affect tolerability. The morning dosing of the XL formulation, in particular, limits drug peak levels during evening hours¹⁰ and may thus explain lower risk of insomnia in our patient

It is illegal to post this copyrighted PDF on any website

Figure 4. Frequency of Peak Plasma Concentrations With Each Formulation of Bupropion^a



^aReprinted with permission from Fava et al.¹⁰

Abbreviations: IR = immediate release, SR = sustained release, XL = extended release.

sample. Assuming a bedtime approximately 14 hours after the first dose, the median time from last dose to bedtime was 4.5 hours for bupropion IR and 8 hours for bupropion SR. While all formulations of bupropion showed a good antidepressant effect, our experience suggests a possible antidepressant advantage for an early morning administration of the slow-release, long-acting XL preparation in patients experiencing insomnia. If the IR formulation is chosen, it is recommended that the final dose not be administered after 2 PM or 3 PM to avoid peak levels in the evening. The last dose of the IR and SR formulations should be taken as early as possible to prevent peak plasma levels in the evening (Figure 4).

Limitations of this study include the retrospective approach, the male predominance of the referral population, an inability to ensure proper medication adherence, and lack of a control group. It is becoming increasingly apparent that the relationship between insomnia and other psychiatric disorders such as depression is complex, at times bidirectional, and incompletely characterized. Insomnia can constitute an independent risk factor for depression, precede the onset of depression, develop in conjunction with other symptoms of depression, and complicate the treatment response. The recognition of such associations underscores the need for randomized, controlled prospective studies.

Conclusion

In this retrospective study, the introduction of bupropion IR or SR for antidepressant purposes was associated with significantly more insomnia compared to the XL dosage form. This finding is most likely attributable to differences in the pharmacokinetics of the formulations. Total exposure (area under the curve) at steady-state of all 3 formulations is equivalent, and all 3 formulations have similar peak concentrations (C_{max}). However, by utilizing an XL dosage form, the patient is exposed to 1 daily peak exposure at a later time (T_{max}) compared to 2 and 3 daily peak exposures for the SR and IR dosage forms, respectively. Further, morning

administration of bupropion XL is associated with a lower evening plasma concentration compared to the SR dosage form; as adverse effects have been associated with plasma levels, a lower evening concentration may result in lower rates of insomnia. Physicians should be aware of such differences when assessing insomnia in patients treated with shorter-acting bupropion formulations and should consider the XL formulation used once daily in the morning to lower disordered sleep while maintaining antidepressant efficacy.

Published online: February 18, 2021.

Potential conflicts of interest: None.

Funding/support: None.

Supplementary material: See accompanying pages.

REFERENCES

- Huecker MR, Smiley A, Saadabadi A. Bupropion. In: *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; 2020. <https://www.ncbi.nlm.nih.gov/books/NBK470212/>.
- Bayard M, Bailey B, Acharya D, et al. Bupropion and restless legs syndrome: a randomized controlled trial. *J Am Board Fam Med*. 2011;24(4):422–428.
- McCarter SJ, Howell MJ. Importance of rapid eye movement sleep behavior disorder to the primary care physician. *Mayo Clin Proc*. 2016;91(10):1460–1466.
- Thase ME, Haight BR, Richard N, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J Clin Psychiatry*. 2005;66(8):974–981.
- Stahl SM, Pradko JF, Haight BR, et al. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry*. 2004;6(4):159–166.
- Hamilton MJ, Smith PR, Peck AW. Effects of bupropion, nomifensine and dexamphetamine on performance, subjective feelings, autonomic variables and electroencephalogram in healthy volunteers. *Br J Clin Pharmacol*. 1983;15(3):367–374.
- Morin CM. Insomnia Severity Index (ISI) [Database record]. APA PsychNet website. <https://doi.org/10.1037/t07115-000>. 1993.
- Zimmerman M, Chelminski I, McGlinchey JB, et al. A clinically useful depression outcome scale. *Compr Psychiatry*. 2008;49(2):131–140.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14(6):540–545.
- Fava M, Rush AJ, Thase ME, et al. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry*. 2005;7(3):106–113.

Supplementary material follows this article.



THE PRIMARY CARE COMPANION FOR CNS DISORDERS

Supplementary Material

Title: Development of Insomnia Associated With Different Formulations of Bupropion

Author(s): Kamal Gandotra, MD; George E. Jaskiw, MD; Scott G. Williams, MD;
Matthew A. Fuller, PharmD; Peijun Chen, MD; Brigid Wilson, PhD;
Rawad ElGhoul, MD; Eric Konicki, MD; and Kingman Perkins Strohl, MD

DOI Number: <https://doi.org/10.4088/PCC.20br02621>

List of Supplementary Material for the article

Appendix 1. Insomnia Severity Index

Appendix 2. Clinically Useful Depression Outcome Scale

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1. Insomnia Severity Index^a

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 + 6 + 7) = _____ your total score

Total score categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

^aReprinted with permission from Charles M. Morin, PhD. (Morin CM. Insomnia Severity Index (ISI) [Database record]. APA PsycInfo website. <https://doi.org/10.1037/107115-000>. 1993).

Appendix 2. Clinically Useful Depression Outcome Scale^a

INSTRUCTIONS

This questionnaire includes questions about symptoms of depression. For each item please indicate how well it describes you during the PAST WEEK, INCLUDING TODAY. Circle the number in the columns next to the item that best describes you.

RATING GUIDELINES

0=not at all true (0 days)

1=rarely true (1-2 days)

2=sometimes true (3-4 days)

3=often true (5-6 days)

4=almost always true (every day)

During the PAST WEEK, INCLUDING TODAY....

- | | | | | | |
|-----------------------------------------------------------------------|---|---|---|---|---|
| 1. I felt sad or depressed..... | 0 | 1 | 2 | 3 | 4 |
| 2. I was not as interested in my usual activities | 0 | 1 | 2 | 3 | 4 |
| 3. My appetite was poor and I didn't feel like eating..... | 0 | 1 | 2 | 3 | 4 |
| 4. My appetite was much greater than usual | 0 | 1 | 2 | 3 | 4 |
| 5. I had difficulty sleeping..... | 0 | 1 | 2 | 3 | 4 |
| 6. I was sleeping too much..... | 0 | 1 | 2 | 3 | 4 |
| 7. I felt very fidgety, making it difficult to sit still..... | 0 | 1 | 2 | 3 | 4 |
| 8. I felt physically slowed down, like my body was stuck in mud | 0 | 1 | 2 | 3 | 4 |
| 9. My energy level was low | 0 | 1 | 2 | 3 | 4 |
| 10. I felt guilty | 0 | 1 | 2 | 3 | 4 |
| 11. I thought I was a failure | 0 | 1 | 2 | 3 | 4 |
| 12. I had problems concentrating..... | 0 | 1 | 2 | 3 | 4 |
| 13. I had more difficulties making decisions than usual | 0 | 1 | 2 | 3 | 4 |
| 14. I wished I was dead..... | 0 | 1 | 2 | 3 | 4 |
| 15. I thought about killing myself..... | 0 | 1 | 2 | 3 | 4 |
| 16. I thought that the future looked hopeless | 0 | 1 | 2 | 3 | 4 |

17. Overall, how much have symptoms of depression interfered with or caused difficulties in your life during the past week?

- 0) not at all
- 1) a little bit
- 2) a moderate amount
- 3) quite a bit
- 4) extremely

18. How would you rate your overall quality of life during the past week?

- 0) very good, my life could hardly be better
- 1) pretty good, most things are going well
- 2) the good and bad parts are about equal
- 3) pretty bad, most things are going poorly
- 4) very bad, my life could hardly be worse

^aReprinted with permission from Mark Zimmerman, MD. Copyright © 2008,

Mark Zimmerman, MD. All rights reserved.