Delayed Onset Urticaria in Depressive Patients with Bupropion Prescription: A Nationwide Population-Based Study

Li-Yu Hu1,2,4,17*, Chia-Jen Liu3,4,5, Ti Lu1, Tsung-Ming Hu2, Chia-Fen Tsai6,17, Yu-Wen Hu4,7, Cheng-Che Shen8,17, Yu-Sheng Chang9,10, Mu-Hong Chen6, Chung-Jen Teng11,17, Huey-Ling Chiang12,13, Chiu-Mei Yeh14, Vincent Yi-Fong Su15, Wei-Shu Wang5,17, Pan-Ming Chen16, Tzeng-Ji Chen14,17, Tung-Ping Su6,17*

1 Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, 2 Department of Psychiatry, Yuli Veterans Hospital, Yuli, Taiwan, 3 Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, 4 Institute of Public Health, National Yang-Ming University, Taipei, Taiwan, 5 Department of Internal Medicine, National Yang-Ming University Hospital, Yilan, Taiwan, 6 Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan, 7 Cancer Center, Taipei Veterans General Hospital, Taipei, Taiwan, 8 Department of Psychiatry, Chiayi Branch, Taichung Veterans General Hospital, Chiayi, Taiwan, 9 Division of Allergy, Immunology, and Rheumatology, Department of Internal Medicine, Shuang Ho Hospital, New Taipei City, Taiwan, 10 Taipei Medical University, New Taipei City, Taiwan, 11 Division of Oncology and Hematology, Department of Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan, 12 Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan, 13 Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan, 14 Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, 15 Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, 16 Department of Psychiatry, Su-Ao and Yuanshan Branch, Taipei Veterans General Hospital, Taipei, Taiwan, 17 National Yang-Ming University, Taipei, Taiwan

Abstract

**Background:** Bupropion, which is widely used in patients with depressive disorder, may cause allergic reactions. However, the real prevalence of these side effects may be overlooked and underreported due to the delayed onset phenomenon.

**Objective:** This study aimed to estimate the real incidence of bupropion-induced urticaria and clarify the delayed onset phenomenon.

**Methods:** We conducted a nationwide cohort study between 2000 and 2009 using Taiwan’s National Health Insurance Dataset. Among 65,988 patients with depressive disorders, we identified new users of bupropion with depressive disorders (bupropion cohort, n = 2,839) and matched them at a ratio of 1:4 regarding age and sex (non-bupropion matched cohort, n = 11,356). The risk of urticaria was compared between the two cohorts.

**Results:** The risk of urticaria occurrence was higher in bupropion users than in matched controls within 4 weeks of starting the medication (risk ratio 1.81; 95% confidence interval 1.28–2.54; \( p = 0.001 \)). The occurrence of urticaria in the bupropion cohort were more frequent on Days 15–28 than Day 1–14 (\( p = 0.002 \)). Cox proportional hazards model showed that a history of urticaria was an independent risk factor for developing bupropion-induced urticaria.

**Conclusions:** Of the antidepressants, bupropion may pose a higher risk of drug-induced urticaria, and this condition might be ignored due to the delayed onset phenomenon. Depressive patients with a history of urticaria are at higher risk of the adverse drug reaction. This study emphasizes the need for increased clinical awareness of this adverse outcome to bupropion use.

Citation: Hu L-Y, Liu C-J, Lu T, Hu T-M, Tsai C-F, et al. (2013) Delayed Onset Urticaria in Depressive Patients with Bupropion Prescription: A Nationwide Population-Based Study. PLoS ONE 8(11): e80064. doi:10.1371/journal.pone.0080064

Editor: James M Wright, University of British Columbia, Canada

Received May 14, 2013; Accepted October 8, 2013; Published November 14, 2013

Copyright: © 2013 Hu et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This study was supported by grants from Taipei Veterans General Hospital (V102D-001-1 and V102D-001-2) and Yuli Veterans Hospital (VHYL-102-08). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

* E-mail: tomsu0402@gmail.com

☯ These authors contributed equally to this work.
Introduction

Bupropion hydrochloride is a popular psychotropic drug that inhibits norepinephrine and dopamine reuptake with minimal effect on serotonin. It is prescribed to millions of patients worldwide for the treatment of major depressive disorders and bipolar depression. In 1997, bupropion was approved by the U.S. Food and Drug Administration (FDA) for use as a smoking cessation aid[1,2].

The U.S. prescribing information for bupropion discloses serious allergic reactions as potential side effects, including urticaria, angioedema, erythema multiforme, Stevens-Johnson syndrome, and even anaphylactic shock. However, these allergic reactions have been rarely reported with bupropion[3]. Two large-scale studies were designed to examine the safety of bupropion as a treatment for smoking cessation in England and France, respectively[4,5]; however, assessment of allergic reactions was not emphasized in these studies. In addition, adverse effects of bupropion in depressive patients, which had been highly associated with urticaria[6], is rarely mentioned in the literature.

To date, only case reports have described bupropion-induced allergic reactions, and it is important to note that clinical features of delayed onset urticaria seems to be present in most of these patients[7-10]. Some studies have postulated that delayed onset urticaria may be overlooked and underreported[9,11] because patients who take bupropion may receive treatment for bupropion-induced delayed onset urticaria by other physicians or hospitals[9,11].

To address these inadequacies in the literature and to assess the pattern of bupropion-induced urticaria, we designed a nationwide population-based study to investigate the actual incidence and timing of new onset urticaria in patients with depression who receive bupropion prescriptions.

Patients and Methods

Data Sources

The Taiwan National Health Insurance (NHI) program offers a comprehensive, unified, and universal health insurance program to all citizens. The NHI program covers more than 96% of the country’s population and has contracted with 99% of all hospitals and clinics in Taiwan[12]. The NHI dataset covers comprehensive medical care, including complete data on outpatient visits, hospitalizations, diagnostic codes, examinations, and prescriptions. Multiple NHI databases (e.g., NHI enrolment files, claims data, and prescription drug registry) are managed and publicly released by the National Health Research Institute, Taiwan. The Bureau of National Health Insurance and the National Health Research Institute regulations guarantee patient confidentiality, and data that may have contained identifiable information were encrypted. Our study received full review by our local institutional review board (Veterans General Hospital Institutional Review Board NO.: 2013-01-035BC) and our institutional review board has waived the need for written informed consent from the participants.

Patient Population

We conducted a retrospective cohort study from January 1, 2000 to December 31, 2009. The presence of depressive disorders was defined as any defined in the International Classification of Diseases, 9th revision, and the clinical modification (ICD-9-CM) codes 296.2X-296.3X, 300.4, and 311.X[13,14]. We also collected information on all types of antidepressants which were available in Taiwan. Antidepressants were classified according to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification.

For the study cohort, we identified 65,988 patients with depressive disorders who had received a first prescription for antidepressants (ATC code N06A) available in Taiwan between January 1, 2000 and December 31, 2009. Patients with a new prescription of bupropion were assigned to the bupropion cohort. Patients who had received bupropion before 2000 or under 20 years of age were excluded. We used the date on which the bupropion treatment was first prescribed as the index date. Within the same observational period, for each of the 2,839 depressive patients taking bupropion, 4 insured people in the comparison cohort with other antidepressants use matched for age, sex, comorbidities, and index date were selected. The same exclusion criteria were applied to the matched comparison cohort. The other antidepressants used in the comparison cohort included fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine maleate, venlafaxine, duloxetine, milnacipran, mirtazapine, trazodone, moclobemide, imipramine, amitriptyline, doxepin, maprotiline, clomipramine, dothiepin. The comparison group included 11,356 patients. In our study, the follow-up began on the index date and will end on 4 weeks later.

We defined patients with an urticaria occurrence as those under ICD-9-CM codes 708.x within 4 weeks of receiving a bupropion prescription. Patients with recent urticaria within one month before receiving the new prescription of bupropion were excluded from the study. A history of urticaria was defined as urticaria occurring at least one month before the index date. The medical history could be traced because the NHIRD in Taiwan was established in 1996.

Patient comorbidities at baseline were identified. Comorbidities included autoimmune diseases (ICD-9-CM code 279.x), liver diseases (ICD9-CM codes 570-573), diabetes mellitus (ICD-9-CM codes 250), chronic kidney diseases (ICD-9-CM codes 580-593), and HIV/AIDS (ICD-9-CM code 042).

Each study patient was tracked until one of the following conditions was met: a diagnosis of urticaria (ICD-9-CM codes 708.x), follow-up was censored at the time of loss to follow-up, death, the patient withdrew from the NHL, or the follow-up period elapsed (4 weeks after index date).

In addition, to clarify whether other antidepressants could have the same delayed onset phenomenon on urticaria occurrence, we compared urticaria occurrence in patients receiving a new bupropion prescription with patients receiving new prescriptions for all other antidepressants available in Taiwan within the next four weeks as a further analysis.
Statistical Analyses

Urticaria occurrence was considered as the primary outcome variable in this study and was calculated for two different time periods after the depressive patients receiving the new antidepressants prescription, i.e., Day 1–14 and Day 15–28. We first compared the distribution of demographic characteristics between the bupropion cohort and the comparison group using the Mann-Whitney U test for median age and using χ² test for sex and baseline comorbidities. The cumulative incidence of urticaria for the two cohorts were calculated by the Kaplan-Meier method, with the log-rank test being used to examine differences between cohorts. Cox proportional hazards model was used to identify risk factors for urticaria occurrence in depressive patients with bupropion prescription within four weeks. We implemented in both the univariate and multivariable fashion to identify risk factors for the urticaria occurrence after bupropion use. Variables included in the model were sex, age, comorbidities, and history of urticaria. The qualifying criterion for inclusion in the multivariate analysis was a result in the univariate-analysis with a P value of less than 0.1. In constructing Cox models, the follow-up began on the index date. The study patients who withdrew (including those who died) from the NHI program were censored. If the patient did not leave the NHI program and encountered no urticaria occurrence, the date of censoring was the date of the end of follow-up. We validated the Cox regression model by checking whether the assumption of proportionality held. The results of Scaled Schoenfeld Residuals test shown the proportionality of hazards assumption was met in this analysis (Table S1). Finally, in order to make the diagnosis of urticaria more specific, the subgroup of urticaria patients diagnosed by dermatologic specialists were determined.

The Perl programming language (version 5.12.2) extracted and computed data. Microsoft SQL Server 2005 (Microsoft Corp., Redmond, WA, USA) was used for data linkage, processing, and control sampling. IBM SPSS (version 19.0 for Windows; IBM Corp., New York, NY, USA) and SAS statistical software (version 9.2; SAS Institute Inc., Cary, NC, USA) were used for all statistical analyses. Results of comparisons with a P value less than .05 were considered statistically significant.

Results

Study Population Characteristics

Characteristics of patients in the bupropion and comparison cohort are shown in Table 1. Of the study population, 2,839 of 65,988 (4.3%) patients with depressive disorders had received bupropion and 11,356 of 65,988 (17.2%) patients were selected to match the bupropion cohorts based on age and sex from January 1, 2000 to December 31, 2009. The median age of the subjects was 41 years (interquartile range: 31–52 years). The majority of patients in both cohorts were female (60.16%). Liver diseases and diabetes mellitus, found in 33.3% and 20.3% of patients, respectively, were the two most common observed comorbidities. A past history of urticaria was recorded in 31.32% of patients. There were no baseline statistical differences in comorbidities and history of urticaria between the groups.

Incidence of Urticaria

Figure 1 shows the cumulative incidences of urticaria occurrence across all participants. The urticaria risk within 4 weeks was significantly higher for patients in the bupropion cohort (cumulative incidence, 16.56‰) than for patients in the comparison cohort (9.16‰) (risk ratio, 1.81; 95% CI 1.28–2.54, p = 0.001) (Table 2). We also stratified patients by age and gender and found that bupropion use was associated with higher urticaria risk in patients under 40 years of age (risk ratio, 2.25; 95% CI 1.41–3.60, p < 0.001), but not in patients over 40 years of age. The use of bupropion was associated with a higher risk of urticaria occurrence in both males and females.

Early and Delayed Onset Urticaria

As shown in Table 3, we compared the cumulative incidences of urticaria occurrence in the Day 1–14 and the Day 15–28 between bupropion and matched cohorts. The results indicated that delayed onset urticaria occurred more frequently for patients in the bupropion cohort (cumulative incidence, 11.98‰) than for patients in the non-bupropion cohort (5.11‰) (risk ratio, 2.34; 95% CI 1.54–3.57, p < 0.001).

Risks Factors for Urticaria

We next performed univariate and multivariable analyses to predict urticaria development in the bupropion cohort (Table 4). We found that a history of urticaria (HR 3.03, 95% CI 1.7–5.4, p < 0.001) was the only independent risk factor for urticaria occurrence following bupropion use.
Delayed onset Urticaria in depressive patients with all types of newly antidepressants prescription

To clarify whether other antidepressants could have the same delayed onset phenomenon on urticaria occurrence, we compared the cumulative incidences of urticaria in depressive patients with patients receiving all other types of new antidepressant prescriptions in Taiwan (Table 5). Bupropion-associated urticaria occurred more frequently on Day 15–28 (11.98‰) than on Day 1–14 (4.58‰) (risk ratio, 2.62; 95% CI 1.38–4.95, \( p = 0.002 \)). Among all antidepressants, the delayed-onset phenomenon was only observed in bupropion users.

Urticaria patients among both cohorts diagnosed by dermatologic specialists

In this subgroup of dermatologist-diagnosed urtiacria among both cohorts, the higher risk for overall urticaria occurrence was similar to the results of the urtiacria patients diagnosed by general practitioners in the bupropion cohort. The bupropion use was still associated with higher urticaria risk in patients under 40 years of age (risk ratio, 2.95; 95% CI 1.48–5.86, \( p = 0.001 \)), but not in patients over 40 years of age. The higher risk of urticaria occurrence in the bupropion cohort was significant in males but not in females (risk ratio, 1.47; 95% CI 0.74–2.92, \( p = 0.273 \)). In addition, the delayed onset trend of urticaria occurrence was still found in this subanalysis (risk ratio, 2.73; 95% CI 1.42–5.25, \( p = 0.002 \)). Detailed results are shown in the Tables S2-S3.

Discussion

To the best of our knowledge, the present study is possibly the largest study to analyze urticaria risk in patients with...
Table 2. Incidence of urticaria occurrence in depressive patients within the first 4 weeks of taking the antidepressants.

| Variables | Bupropion cohort | Matched cohort | Risk ratio | p value |
|-----------|------------------|----------------|------------|---------|
| Age       | n (%)            | n (%)          | (95% CI)   |         |
| < 40      | 27(21.16)        | 48(40.0)       | 2.25(1.41–3.60) | < 0.001 |
| 40–59     | 15(14.29)        | 39(29.29)      | 1.54(0.85–2.78) | 0.151   |
| ≥ 60      | 9(9.75)          | 17(13.28)      | 1.18(0.44–3.17) | 0.748   |
| Sex       |                  |                |            |         |
| Male      | 16(14.15)        | 33(27.29)      | 1.44(1.07–1.94) | 0.008   |
| Female    | 31(18.15)        | 71(10.39)      | 1.75(1.29–2.35) |         |

CI: confidence interval

Table 3. Comparisons of early and delayed onset urticaria occurrence.

| Variables | Bupropion cohort | Matched cohort | Risk ratio | p value |
|-----------|------------------|----------------|------------|---------|
| Age       | n (%)            | n (%)          | (95% CI)   |         |
| Total     | 47(16.66)        | 104(9.16)      | 1.81(1.28–2.54) | 0.001   |
| Early onset (Day 1–14) | 13(4.58)    | 46(4.05)       | 1.13(0.61–2.09) | 0.696   |
| Delayed onset (Day 15–28) | 34(11.98)  | 56(5.11)       | 2.34(1.54–3.57) | <0.001  |

Table 4. Analyses of risk factors for urticaria in depressive patients after bupropion use.

| Variables | Univariate analysis | Multivariable analysis |
|-----------|---------------------|------------------------|
|           | HR                  | 95% CI                 | p value | HR          | 95% CI | p value |
| Age       | 0.98                | 0.96–1.00              | 0.101   | 0.99        | 0.97–1.01 | 0.367   |
| Male sex  | 0.78                | 0.43–1.43              | 0.424   |             |         |         |
| Comorbidities |                   |                        |         |             |         |         |
| Autoimmune diseases | 0.75          | 0.27–2.09              | 0.580   |             |         |         |
| Liver diseases | 0.74           | 0.39–1.40              | 0.358   |             |         |         |
| Diabetes mellitus | 0.35          | 0.13–0.98              | 0.046   | 0.38        | 0.13–1.10 | 0.075   |
| Chronic kidney disease | 1.59          | 0.74–3.40              | 0.232   |             |         |         |
| AIDS      | 0.05                | 0.00–2.12x10^-13      | 0.861   |             |         |         |
| History of urticaria | 2.94          | 1.65–5.24              | <0.001  | 3.02        | 1.69–5.39 | <0.001  |

HR: hazard ratio, CI: confidence interval, AIDS: acquired immunodeficiency syndrome.

Several smaller reports have shown that nearly all of the antidepressants seemed to be associated with an onset of urticaria, including fluoxetine[15], paroxetine[16], sertraline[17], escitalopram[17], venlafaxine[18], bupropion[5,7,9,10,19-25], mirtazapine[18], and tricyclic antidepressants[26]. However, very few attempts have been made to compare the occurrence of urticaria among the various antidepressants. In our study, the results showed that bupropion use was associated with the highest risk of urticaria development and the delayed onset phenomenon of urticaria occurrence was only shown in the bupropion users compared with all other antidepressant prescriptions in Taiwan assessed.

In addition to bupropion-induced urticaria[21-23], many smaller studies have described a relationship between bupropion use and allergic reactions, including angioedema[20], erythema multiform[24], Stevens-Johnson syndrome[27], and serum sickness-like reactions[7-11,25]. Moreover, most of the studies noticed delayed onset characteristics of these allergic reactions. Although some researchers had presumed that the bupropion-induced urticaria may be underestimated[9,11], unanswered reasons still remain. According to our results, we hypothesized that the reason of underestimation may be related to the delayed onset phenomenon of bupropion-induced urticaria. In addition, bupropion-induced urticaria seldom develops alone and is
sometimes accompanied with other more serious allergic reactions, including angioedema\cite{19,20}, arthralgia\cite{8}, serum sickness-like reaction\cite{7,9-11}, or symptoms of anaphylaxis, which may indicate a medical emergency. Therefore, if medical personnel do not recognize the adverse drug reaction, then patients could be put at risk for more severe drug hazards.

The mechanisms of urticaria are thought to be associated with histamine and other mediators being released from mast cells and basophils. The higher occurrence of bupropion-induced urticaria in younger patients could be explained by immunosenescence, which is an age-related decline in immune functions. It has been reported that mast cell development declines through the aging process\cite{28}, and the number of dermal mast cells decreases with age in human subjects\cite{29}. However, the mechanism of bupropion-induced urticaria is currently unknown. We hypothesize that the adverse drug reaction may be linked to the structure of bupropion, which is chemically similar to amfepramone. Amfepramone is considered a selective norepinephrine releasing agent, and norepinephrine may play an important role in adrenergic urticaria, which is considered to be a form of neurogenic reaction that is mainly triggered by stress. Moreover, in recent years, bupropion has been suggested to have effects as an anti-inflammatory agent by down-regulating tumor necrosis factor synthesis, which may slow the course of some inflammatory processes\cite{30,31}. Therefore, we hypothesized that the anti-inflammatory effect may delay the allergic reaction and lead to delayed onset urticaria.

While urticaria may be confused with a variety of other dermatologic diseases that are similar in appearance and are also pruritic, it is possible that other urticaria-like skin reactions may have been misclassified under the code based on claims data. In order to make the diagnosis more specific, subgroup of the urticaria diagnosed by dermatologic specialists in our study group were further analyzed and the higher risk for overall urticaria occurrence and delayed onset trend were similar to the results of the urtiacria patients diagnosed by general practitioners in the bupropion cohort.

Several limitations inherent in using claims databases also need to be taken into consideration. First, because patients’ identifications were blocked for protection of privacy, we have no way to assess for actual intake of prescribed antidepressants. However, such a limitation usually leads toward an under-estimation of risk. Besides, although no evidence has shown that the difference of drug compliance between bupropion and other antidepressants, it is reasonable
to assume that the higher risk of delayed onset urticaria in the bupropion cohort may be associated with the influence of drug compliance. Second, drugs which may cause were not adjusted for. Although urticaria is really often caused by the many drugs including antibiotics and anticonvulsants use in our clinical experience. However, these drugs were not selected for adjustment in this study because the antibiotics and anticonvulsants were less common co-medications used by our study subjects (patients with depressive disorders). Besides, the frequency of antibiotics and anticonvulsants co-prescriptions with antidepressants is relatively low during a short follow-up period (4 weeks) in our study. Third, a number of other potential confounding factors that might affect urticaria risk were not available in the reimbursement data used in this study, such as psychosocial stresses, foods, family history of urticaria, recent travel history, exposure to environmental stimulants and smoking[32]. {Stockli, 2007 #51}Among these non-observable confounders, for the reason that the use of bupropion may be helpful to depressive patients who smoke[33], therefore, smoking may be an important non-observable confounder in our study. Finally, further investigations are needed to explore such associations in different populations and ethnic groups. In conclusion, our study has found that patients with depressive disorders who received bupropion were at an unusually higher risk for delayed onset urticaria. Based upon our data, we suggest that more attention should be focused on the bupropion-induced urticaria in patients with depressive disorders and urge caution over the delayed onset phenomenon, especially in patients under 40 years of age and with past history of urticaria, in order to avoid more severe drug allergies as a result of prescribing the same drugs. Although more research is needed, this article serves to broaden physicians’ knowledge base when prescribing bupropion.

Supporting Information

Table S1. Scaled Schoenfeld residuals test of proportional hazards. (DOC)

Table S2. Incidence of dermatologist-diagnosed urticaria occurrence in depressive patients within first 4 weeks. (DOC)

Table S3. Comparisons of early and delayed onset dermatologist-diagnosed urticaria occurrence. (DOC)

Acknowledgements

We thank Huei-Sing Chang and Cheng-Fang Hong for technical support.

Author Contributions

Conceived and designed the experiments: LYH CJL TPS. Performed the experiments: LYH CJL TMH CCS CMY TPS. Analyzed the data: LYH CJL CMY TL. Contributed reagents/materials/analysis tools: TMH CFT YWH YSC PMC. Performed the experiments: LYH CJL TMH CCS CMY TPS. Analyzed the data: LYH CJL CMY TL. Contributed reagents/materials/analysis tools: TMH CFT YWH YSC PMC. Wrote the manuscript: LYH CJL MHC HLC TL. English editing: YSC CJT VYFS WSW.

References

1. Crain D, Bhat A (2010) Current treatment options in smoking cessation. Hosp Pract (Minneap) 38: 53-61. doi:10.3810/hp.2010.02.279. PubMed: 20469625.
2. Sheng LX, Tang YL, Jiang ZN, Yao CH, Gao JY et al. (2012) Sustained-Release Bupropion for Smoking Cessation in a Chinese Sample: A Double-Blind, Placebo-Controlled Randomized Trial. Nicotine Tob Res.
3. Fava M, Rush AJ, Thase ME, Clayton A, Stahl SM et al. (2005) 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. Prim Care Companion J Clin Psychiatry 7: 106–113. doi:10.4088/PCC.v07n0305. PubMed: 16027785.
4. Boshier A, Wilton LV, Shakir SA (2003) Evaluation of the safety of bupropion (Zyban) for smoking cessation from experience gained in general practice in England in 2000. Eur J Clin Pharmacol 59: 767–773. doi:10.1007/s00228-003-0693-0. PubMed: 14615857.
5. Beyens MN, Guy C, Mounier G, Laborte S, Ollagnier M (2008) Serious adverse reactions of bupropion for smoking cessation: analysis of the French Pharmacovigilance Database from 2001 to 2004. Drug Saf 31: 1017–1026. doi:10.2165/00002018-200831110-00006. PubMed: 18840021.
6. Staubach P, Dechene M, Metz M, Magehr L, Siebenhaar F et al. (2011) High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. Acta Derm Venereol 91: 557-561. PubMed: 21597672.
7. Peloso PM, Baillie C (1999) Serum sickness-like reaction with bupropion. JAMA 282: 1817. doi:10.1001/jama.282.19.1817. PubMed: 10573271.
8. Ornetti P, Disson-Dautriche A, Muller G, Cherasse A, Tavernier C et al. (2004) Joint symptoms in patients on bupropion therapy. Joint Bone Spine 71: 583-585. doi:10.1016/j.jbspin.2003.10.004. PubMed: 15589445.
9. McCollom RA, Elbe DH, Ritchie AH (2000) Bupropion-induced serum sickness-like reaction. Ann Pharmacother 34: 471-473. doi:10.1345/aph.19297. PubMed: 10772432.
10. Tripathi A, Greenberger PA (1999) Bupropion hydrochloride induced serum sickness-like reaction. Ann Allergy Asthma Immunol 83: 165–166. doi:10.1016/S1081-1206(10)62630-0. PubMed: 10480592.
11. Hack S (2004) Pediatric bupropion-induced serum sickness-like reaction. J Child Adolesc Psychopharmacol 14: 478-480. doi:10.1089/cap.2004.14.475. PubMed: 15650506.
12. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN et al. (2012) Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. JAMA 308: 1906-1914. doi:10.1001/2012.jama.11975. PubMed: 23162861.
13. Huang KL, Su TP, Chen TJ, Chou YH, Bai YM (2009) Comorbidity of cardiovascular diseases with mood and anxiety disorder: a population based 4-year study. Psychiatry Clin Neurosci 63: 401-409. doi:10.1111/j.1440-1819.2009.01974.x. PubMed: 19566773.
14. Wu CS, Wang WC, Cheng YC, Gau SS (2011) Association of cerebrovascular events with antidepressant use: a case-crossover study. Am J Psychiatry 168: 511-521, doi:10.1176/ajp.2010.10071064. PubMed: 21406464.
15. McGregor RA, Rolfe F, Mausset J, Lavignic C, Bonnetblanc JM (1995) Urticarial vasculitis induced by fluoxetine. Dermatology 191: 164. doi:10.1159/0002346539. PubMed: 8520306.
16. Welsh JP, Cusack CA, Ko C (2006) Urticarial vasculitis secondary to paroxetine. J Drugs Dermatol 5: 1012-1014. PubMed: 17373154.
17. Dadić-Hero E, Ružić K, Graovac T, Graovac M, Palijan TZ et al. (2011) Allergic reactions–outcome of sertraline and escitalopram treatments. Psychiatry Danub 23: 120-122. PubMed: 21448115.
18. Lin CE, Chen CL (2010) Repeated angioedema following administration of venlafaxine and mirtazapine. Gen Hosp Psychiatry 32: 341: e341-e342. PubMed: 20430242.
19. Bhella R, Southgate J (2010) Angioedema caused by bupropion treatment. Acute Med 9: 70-72. PubMed: 21597575.
20. Tackett AE, Smith KM (2008) Bupropion-induced angioedema. Am J Health Syst Pharm 65: 1627-1630. doi:10.2146/ajhp070575. PubMed: 18714109.
21. Loo WJ, Alexandroff A, Flanagan N (2003) Bupropion and generalized acute urticaria: a further case. Br J Dermatol 149: 660. doi:10.1046/j.1365-2133.2003.05508.x. PubMed: 12534623.
22. Chiavérini C, Baldin B, Chichmanian RM, Ortonne JP, Lacour JP (2003) Bupropion and generalized acute urticaria: eight cases. Br J Dermatol 148: 177-178. doi:10.1046/j.1365-2133.2003.05083.x. PubMed: 12534623.
23. Busse PJ, Mathur SK (2010) Age-related changes in immune function: effect on airway inflammation. J Allergy Clin Immunol 126: 690-700; quiz: 20920759.
24. Milionis HJ, Skopelitou A, Elisaf MS (2000) Hypersensitivity syndrome caused by amitriptyline administration. Postgrad Med J 76: 361-363. doi:10.1136/pgmj.76.686.381. PubMed: 10824052.
25. Surovik J, Riddle C, Chon SY (2010) A case of bupropion-induced Stevens-Johnson syndrome with acute psoriatic exacerbation. J Drugs Dermatol 9: 1010-1012. PubMed: 20684153.
26. van der Meer RM, Willemsen MC, Smit F, Cuijpers P (2013) Smoking cessation interventions for smokers with current or past depression. Cochrane Database Syst Rev 8: CD006102.