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SCIENTIFIC INVESTIGATIONS

Effects of bupropion and SSRI antidepressants on leg movement activity and chin muscle tone during sleep in adolescents

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Study Objectives: To evaluate the effects of bupropion on periodic limb movements during sleep (PLMS) and chin electromyography tone in children taking it for their mood disorder, compared to the effects of selective serotonin reuptake inhibitors (SSRIs) and of bupropion combined with SSRIs.

Methods: Six adolescents (aged 16.0 ± 0.63 years) taking bupropion alone and 6 adolescents (aged 15.9 ± 1.36 years) taking bupropion in combination with an SSRI antidepressant were recruited, along with 10 adolescents (aged 16.2 ± 0.2 years) taking different SSRIs, and they were also enrolled together with 17 age- and sex-matched control patients (aged 15.5 ± 1.26 years). Polysomnographic studies were obtained, and participants' leg movement activity during sleep and muscle tone were assessed quantitatively (atonia index) during all sleep stages.

Results: Participants taking SSRIs showed PLMS indices significantly higher than those of control patients, whereas adolescents taking bupropion showed only slightly increased indexes of nonperiodic leg movements during sleep. No differences in PLMS were observed between adolescents taking bupropion alone or in association with SSRIs. The atonia index showed, within each sleep stage, the lowest values in the 2 groups taking SSRIs and the highest in the control patients; adolescents taking bupropion alone tended to show values slightly smaller than those of the control patients.

Conclusions: We found that similar to adults, in adolescents SSRIs but not bupropion are associated with increased PLMS. Bupropion also seems to counteract the SSRI-induced increase of PLMS, when administered in combination; thus, the dopaminergic effect of bupropion seems to outmatch the antidopaminergic action of SSRIs. Conversely, bupropion does not counteract the effects of SSRIs on chin electromyography tone.

Keywords: bupropion, SSRI antidepressants, periodic leg movements during sleep, leg movement activity during sleep, periodicity index, atonia index, chin EMG tone, adolescents

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BRIEF SUMMARY

Current Knowledge/Study Rationale: In adults, selective serotonin reuptake inhibitors but not bupropion have been reported to affect periodic limb movements during sleep and rapid eye movement sleep atonia. We analyzed the different effects of these 2 classes of antidepressants on periodic limb movements during sleep and chin electromyography tone during sleep in adolescents and evaluated the same measures when they were administered in association.

Study Impact: In adolescents, selective serotonin reuptake inhibitors but not bupropion are associated with increased periodic limb movements during sleep. Bupropion also seems to counteract the selective serotonin reuptake inhibitor–induced increase of periodic limb movements during sleep but not the changes in chin electromyography tone, when administered in combination; thus, the dopaminergic effect of bupropion seems to outmatch the antidopaminergic action of selective serotonin reuptake inhibitors.

INTRODUCTION

Bupropion is a dopamine and norepinephrine reuptake inhibitor commonly indicated for the treatment of major depressive disorder and for smoking cessation and is a promising alternative for the treatment of attention-deficit/hyperactivity disorder (ADHD) in both adolescents and adults.[1] Furthermore, regarding the treatment of major depressive disorder, the combination of bupropion and selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenalin reuptake inhibitors is generally well tolerated, capable of increasing the antidepressant response and reducing the adverse effects associated with SSRIs or serotonin and noradrenalin reuptake inhibitors. For example, the latter can induce long-term adverse effects, such as sexual dysfunction or weight gain[2]; moreover, SSRIs can induce emotional detachment, apathy, or fatigue,[3] whereas bupropion has been reported to be effective on the cluster of depressive symptoms of fatigue, low energy, and hypersomnia and seems to induce these adverse effects less often than SSRIs.[4] In addition, bupropion is not associated with major adverse cardiovascular events,[5] unlike many SSRIs.[6]

A significant association between a large range of movement disorders, such as akathisia, bruxism, dystonia, myoclonus, parkinsonism, tardive dyskinesia, tic, and tremor and the intake of various types of antidepressants has been reported, whereas restless legs syndrome (RLS) seems to be associated only with SSRIs.[7]

RLS is a sleep movement disorder whose etiopathogenesis is still under study; an involvement of the dopaminergic system has been proposed.[8] RLS and periodic leg movements during sleep (PLMS) worsening with some antidepressants, especially SSRIs and mirtazapine, are known phenomena, with the exception of bupropion[9]; however, data regarding the use of bupropion in the treatment of mood disorders in patients with RLS are still scarce.[10]

RLS is very often associated with PLMS, which can also be present in the absence of RLS as a separate sleep movement disorder (periodic limb movement disorder), if associated with sleep or daytime disturbance.[11] In the general population, PLMS have a prevalence of approximately 30%,[12] with 2 peaks, in childhood and in older adults[13]; PLMS can negatively impact the quality of sleep and health status in both children and adults.[14–16] There are no accepted guidelines for the treatment of PLMS; moreover, they are often associated with psychiatric conditions,[16] with consequent worsening of PLMS after treatment with SSRIs, in both adults and children, further complicating the clinical symptomatology of patients with mental disorders and sleep disruption.[17,18]

Despite the high prevalence of both PLMS[12] and psychiatric disorders,[19] studies investigating the effects of antidepressants on PLMS are few (especially in children).[9] Furthermore, PLMS and RLS are very often associated with ADHD, a very frequent pathology in childhood and adolescence,[20,21] in which bupropion has shown good efficacy and good tolerance.[1]

Among all antidepressants, as mentioned above, bupropion has different characteristics in regard to the mechanism of action and the tolerability profile, with only few reports in the literature evaluating its impact on PLMS.

In addition, antidepressants, especially SSRIs and serotonin and noradrenalin reuptake inhibitors, have long been known to be often associated with rapid eye movement (REM) sleep without atonia[22] and less often with REM sleep behavior disorder[23] in adults, in whom antidepressants may act as factors "unmasking" REM sleep behavior disorder without causing it.[22,24] One study recently reported that in children SSRI antidepressants increase the chin electromyography (EMG) tone during REM sleep, similar to adults, and in all nonrapid eye movement (NREM) sleep stages.[25] However, the clinical meaning of this effect in children has yet to be determined.

For all these reasons, the aim of this new study was to evaluate the effects of bupropion on PLMS and chin EMG tone in a small convenience sample of children taking bupropion chronically for their mood disorder, compared to the effects of SSRIs and of bupropion associated with SSRIs.

METHODS

Participants

This study was part of a retrospective chart review from every sleep study performed at Seattle Children's Hospital from June 14, 2020, until December 8, 2021. Participants using antidepressants at the time of polysomnography (PSG) were included. For each patient data collected included age, sex, current use of antidepressant medication, name of medication, and dosage. Among 3,371 children and adolescents, 361 were taking 1 or

Table 1—Sleep variables found in control patients and participants taking SSRIs or bupropion.

	Control Patients (n = 17)	SSRIs (n = 10)	Bupropion (n = 6)	Kruskal–Wallis ANOVA		Mann–Whitney *U* Test, *P* <		
	Median (IQR)	Median (IQR)	Median (IQR)	H_2, n = 33	*P* <	1 vs 2	2 vs 3	1 vs 3
Time in bed, min	476.0 (461.0–505.0)	510.3 (476.5–549.5)	486.8 (480.0–512.0)	2.951	NS	—	—	—
Sleep period time, min	453.0 (439.0–492.0)	470.3 (443.5–504.0)	475.8 (432.5–493.5)	1.091	NS	—	—	—
Total sleep time, min	428.5 (406.0–467.0)	394.3 (326.0–434.0)	401.0 (321.0–432.0)	3.117	NS	—	—	—
Sleep latency, min	10.0 (6.0–13.0)	37.0 (32.0–46.0)	14.8 (5.5–19.0)	11.248	.0036	0.001	0.045	NS
Stage R latency, min	91.5 (67.5–120.5)	123.8 (93.5–157.5)	76.3 (57.5–94.0)	3.762	NS	—	—	—
Stage shifts/h	5.5 (4.4–11.7)	16.4 (12.2–22.9)	12.0 (8.8–15.3)	13.796	.001	0.0007	NS	0.042
Awakenings/h	1.2 (0.8–3.9)	4.2 (3.3–9.5)	5.1 (4.6–5.5)	7.230	.027	0.02	NS	NS
Sleep efficiency, %	91.8 (87.4–93.4)	73.6 (67.8–85.0)	85.1 (78.4–88.1)	8.717	.013	0.0084	NS	NS
Stage W, %	3.9 (2.1–6.0)	18.4 (8.0–28.0)	11.2 (5.9–21.5)	7.703	.021	0.033	NS	0.019
Stage N1, %	5.0 (3.7–5.9)	12.4 (7.9–17.0)	8.6 (4.0–9.7)	10.876	.0043	0.0017	NS	NS
Stage N2, %	51.5 (44.0–55.3)	35.9 (28.5–39.7)	39.1 (36.9–58.0)	7.646	.022	0.0046	NS	NS
Stage N3, %	19.9 (17.8–24.9)	14.8 (12.9–20.8)	12.6 (10.2–16.9)	7.361	.025	NS	NS	0.013
Stage R, %	17.4 (12.3–21.6)	16.6 (8.0–18.7)	19.8 (16.3–21.9)	1.296	NS	—	—	—

ANOVA = analysis of variance, IQR = interquartile range, SSRs = selective serotonin reuptake inhibitors.

more antidepressant medications, and only 14 were taking bupropion. Of these 14 participants, 2 had other sleep/medical disorders and were not included. Consequently, for this study, a convenience group of 6 adolescents (4 girls and 2 boys; mean age, 16.0 years; standard deviation, 0.63) taking bupropion alone (150–300 mg/d) and another convenience sample of 6 adolescents (5 girls and 1 boy; mean age, 15.9 years; standard deviation, 1.36) taking bupropion (150–300 mg/d) in combination with an SSRI antidepressant (3 taking sertraline, 2 taking fluoxetine, and 1 taking escitalopram) was also recruited. In addition, 10 adolescents (6 girls and 4 boys; mean age, 16.2 years; standard deviation, 0.2) taking different SSRIs alone were also enrolled; 4 were taking sertraline (150–200 mg/d), 4 were taking escitalopram (10–30 mg/d), and 2 were taking fluoxetine (10–30 mg/d). Antidepressants were prescribed for depression, anxiety, or both. None of the adolescents had another medical or psychiatric disorder. PSG recording had been ordered, in all patients, because of snoring, fatigue, or sleepiness. Treatment duration ranged between 2 and 12 months. All adolescents had an apnea-hypopnea index < 1 event/h and none were diagnosed with RLS.

Finally, an age- and sex-matched group of 17 control adolescents (13 girls and 4 boys; mean age, 15.5 years; standard deviation, 1.26) was selected from our database (including adolescents recruited by the authors at their respective centers who had participated in previous studies[26]). None of these adolescents were taking drugs or were affected by another medical, psychiatric, or sleep disorder other than primary snoring. In all groups, physical and neurological examinations were conducted. In addition, sleep apnea was ruled out in each patient, independently, by 2 different sleep experts.

The sex composition and age of the groups were not significantly different. No sample size/power analysis was possible because this was a convenience sample. The study was approved by the local ethics committee, and all participants or their parents/guardians provided informed written consent.

PSG recording and scoring of leg movements and of the submentalis muscle EMG amplitude during sleep

Routine full-night PSG recordings in the sleep laboratory were carried out in each participant, including EMG of the submentalis and both tibialis anterior muscles and electrocardiogram. Sleep stages and arousals were visually scored following standard criteria.[27]

Leg movements during sleep (LMS) were detected and scored according to the most recent criteria by the World Association of Sleep Medicine,[28] followed by the calculation of a series of measures including total LMS index; PLMS index; short-interval LMS (SILMS) index; isolated LMS (ISOLMS) index; percentage of bilateral PLMS; periodicity index (PLMS/total LMS ratio); PLMS, SILMS, and ISOLMS durations; and PLMS index in REM sleep and in NREM sleep. In particular, the periodicity index can vary from 0 (complete absence of PLMS within the total LMS activity) to 1 (the entire LMS activity formed by PLMS). Moreover, all sleep leg movement onset-to-onset inter movement intervals (IMIs) IMIs from each recording were counted in each patient for 2-second classes, and group grand averages were obtained and used for statistical analysis. Finally, hourly night-distribution histograms of the number of PLMS during the first 8 recording hours were obtained for each group of participants.

In addition, we computed the atonia index for the quantification of the submentalis muscle EMG amplitude, as previously reported[29–31]; this amplitude has been shown to be a reliable measure also in children and adolescents.[25,31–33] Briefly, the atonia index can vary from 0 (which means the complete absence of EMG atonia) to 1 or continuous stable EMG atonia during each sleep stage.

Table 2—Sleep variables found in participants taking bupropion alone or bupropion in combination with SSRIs.

	Bupropion (n = 6)	Bupropion + SSRIs (n = 6)	Mann–Whitney *U* Test
	Median (IQR)	Median (IQR)	*P* <
Time in bed, min	486.8 (480.0–512.0)	520.7 (489.0–525.5)	NS
Sleep period time, min	475.8 (432.5–493.5)	493.0 (478.0–510.0)	NS
Total sleep time, min	401.0 (321.0–432.0)	419.5 (288.0–469.0)	NS
Sleep latency, min	14.8 (5.5–19.0)	11.5 (10.5–14.5)	NS
Stage R latency, min	76.3 (57.5–94.0)	93.7 (89.5–96.0)	NS
Stage shifts/h	12.0 (8.8–15.3)	14.3 (8.3–20.1)	NS
Awakenings/h	5.1 (4.6–5.5)	4.6 (3.4–5.7)	NS
Sleep efficiency, %	85.1 (78.4–88.1)	83.2 (55.7–95.2)	NS
Stage W, %	11.2 (5.9–21.5)	14.8 (2.9–43.1)	NS
Stage N1, %	8.6 (4.0–9.7)	9.3 (3.9–16.9)	NS
Stage N2, %	39.1 (36.9–58.0)	36.1 (31.9–42.1)	NS
Stage N3, %	12.6 (10.2–16.9)	24.3 (13.1–27.6)	NS
Stage R, %	19.8 (16.3–21.9)	7.7 (6.7–16.0)	NS

IQR = interquartile range, SSRIs, selective serotonin reuptake inhibitors.

Statistical analysis

The nonparametric Kruskal–Wallis analysis of variance was used for between-group comparisons, followed by posthoc comparisons using the Mann–Whitney *U* test. Frequencies were compared using the chi-square test. The commercially available software STATISTICA version 6 (StatSoft Inc., Palo Alto, CA, USA) was used for the statistical analysis, and the significance level was set at $P < .05$.

RESULTS

Table 1 reports the sleep architecture measures found in control patients and patients taking SSRIs or bupropion. Overall, adolescents taking SSRIs showed more variables different from those of control patients than patients taking bupropion, with increased sleep latency, number of stage shifts, and number of awakenings, along with an increased percentage of wakefulness after sleep onset and percentage of sleep stage N1. These differences, together with the decreased sleep efficiency and percentage of sleep stage N2, point at a significant sleep architecture impairment in these patients. Conversely, patients taking bupropion only differed from control patients because of their increased number of awakenings and percentage of stage W sleep, and for a decrease in the percentage of sleep stage N3. With respect to patients taking SSRIs, those taking bupropion had only a significantly shorter sleep latency. When patients taking bupropion were compared to those taking bupropion associated with SSRIs, no significant differences were found regarding sleep architecture (**Table 2**).

Table 3 shows the measures of leg movement activity during sleep found in control patients and patients taking SSRIs or bupropion. Again, participants taking SSRIs showed more variables different from those of control patients than adolescents taking bupropion, with an increase in all indexes and categories of LMS, including the periodicity index. The duration of the different LMS categories (PLMS, SILMS, and ISOLMS) was not different. A similar pattern of difference was evident for the comparison between SSRIs and bupropion, but in this case, only PLMS were clearly more numerous in adolescents taking SSRIs (not SILMS or ISOLMS) because these were also significantly increased in these patients as compared to in the control patients. No significant differences regarding LMS parameters were found between adolescents taking bupropion alone or in association with SSRIs (**Table 4**). In these analyses, data from only 5 participants for each bupropion group were used because of the presence of artifacts in the leg EMG signals in 1 adolescent in each group, which did not allow a reliable use of their data for statistical analysis.

The top panel of **Figure 1** shows the distribution of intervals between consecutive LMS in adolescents taking SSRIs or bupropion and in control patients. Patients taking SSRIs showed 2 clearly increased peaks, one extending from approximately 2–10 seconds and another from 10–60 seconds, respectively, with the second peak essentially representing PLMS and the first peak representing SILMS. Adolescents taking bupropion and control patients (not taking any medication) showed only the

Table 3—Leg movement activity during sleep measures found in control patients and participants taking SSRIs or bupropion.

	Control Patients (n = 17)	SSRIs (n = 10)	Bupropion (n = 5)	Kruskal–Wallis ANOVA		Mann–Whitney *U* Test, *P* <		
	Median (IQR)	Median (IQR)	Median (IQR)	H_2, n = 32	*P* <	1 vs 2	2 vs 3	1 vs 3
PLMS index, n/h	0.6 (0.0–2.1)	13.2 (5.6–15.6)	0.5 (0.0–1.6)	19.391	.0001	0.00004	0.0027	NS
SILMS index, n/h	1.9 (1.7–3.8)	6.4 (4.8–20.6)	5.1 (3.0–6.1)	12.435	.002	0.0012	NS	0.042
ISOLMS index, n/h	7.2 (5.6–9.0)	15.9 (10.3–22.7)	11.8 (9.5–13.6)	14.745	.0006	0.0004	NS	0.034
Total LMS index, n/h	12.3 (7.3–13.8)	34.1 (23.7–47.0)	16.9 (14.6–19.7)	19.887	.0001	0.00003	0.012	NS
Bilateral PLMS, %	0.4 (0.0–0.8)	3.1 (2.0–7.6)	0.2 (0.0–0.3)	18.607	.0001	0.0001	0.0033	NS
Periodicity index	0.092 (0.000–0.118)	0.303 (0.205–0.554)	0.047 (0.000–0.048)	14.573	.0007	0.0008	0.004	NS
PLMS duration, s	2.9 (2.0–3.5)	2.5 (2.3–3.2)	2.3 (1.2–3.1)	0.839	NS	—	—	—
SILMS duration, s	2.3 (2.0–2.8)	2.9 (2.5–3.4)	2.3 (1.9–2.9)	5.621	NS	—	—	—
ISOLMS duration, s	3.1 (2.7–3.3)	2.9 (2.7–3.3)	2.5 (2.1–3.3)	1.056	NS	—	—	—
REM sleep PLMS index, n/h	0.0 (0.0–0.0)	4.5 (3.5–5.7)	0.0 (0.0–0.0)	11.747	.0028	0.013	0.023	NS
NREM sleep PLMS index, n/h	0.7 (0.0–1.7)	15.1 (5.5–17.8)	0.6 (0.0–1.7)	17.777	.0001	0.000081	0.004	NS

ANOVA = analysis of variance, IQR = interquartile range, ISOLMS = isolated leg movements during sleep, LMS = leg movements during sleep, NREM = nonrapid eye movement, PLMS = periodic leg movements during sleep, REM = rapid eye movement, SILMS = short-interval leg movements during sleep, SSRIs = selective serotonin reuptake inhibitors.

Table 4—Leg movement activity during sleep measures found in participants taking bupropion alone or bupropion associated with SSRIs.

	Bupropion (n = 5)	Bupropion + SSRIs (n = 5)	Mann–Whitney *U* Test
	Median (IQR)	Median (IQR)	*P* <
PLMS index, n/h	0.5 (0.0–1.6)	3.4 (1.0–4.3)	NS
SILMS index, n/h	5.1 (3.0–6.1)	2.0 (1.4–2.1)	NS
ISOLMS index, n/h	11.8 (9.5–13.6)	8.9 (5.7–10.2)	NS
Total LMS index, n/h	16.9 (14.6–19.7)	10.9 (9.6–19.1)	NS
Bilateral PLMS, %	0.2 (0.0–0.3)	0.8 (0.6–2.5)	NS
Periodicity index	0.047 (0.000–0.048)	0.129 (0.092–0.356)	NS
PLMS duration, s	2.3 (1.2–3.1)	2.2 (1.7–3.0)	NS
SILMS duration, s	2.3 (1.9–2.9)	2.8 (2.3–2.9)	NS
ISOLMS duration, s	2.5 (2.1–3.3)	3.0 (2.3–3.4)	NS
REM sleep PLMS index, n/h	0.0 (0.0–0.0)	0.0 (0.0–0.0)	NS
NREM sleep PLMS index, n/h	0.6 (0.0–1.7)	3.7 (1.4–4.4)	NS

IQR = interquartile range, ISOLMS = isolated leg movements during sleep, LMS = leg movements during sleep, NREM = nonrapid eye movement, PLMS = periodic leg movements during sleep, REM = rapid eye movement, SILMS = short-interval leg movements during sleep, SSRIs = selective serotonin reuptake inhibitors.

first SILMS peak, which was less evident in the control patients. When adolescents taking bupropion were compared to those taking bupropion associated with SSRIs, no significant difference was found, with the exception of the peak at 4 seconds, which was less evident in the latter group (**Figure 1**, bottom panel).

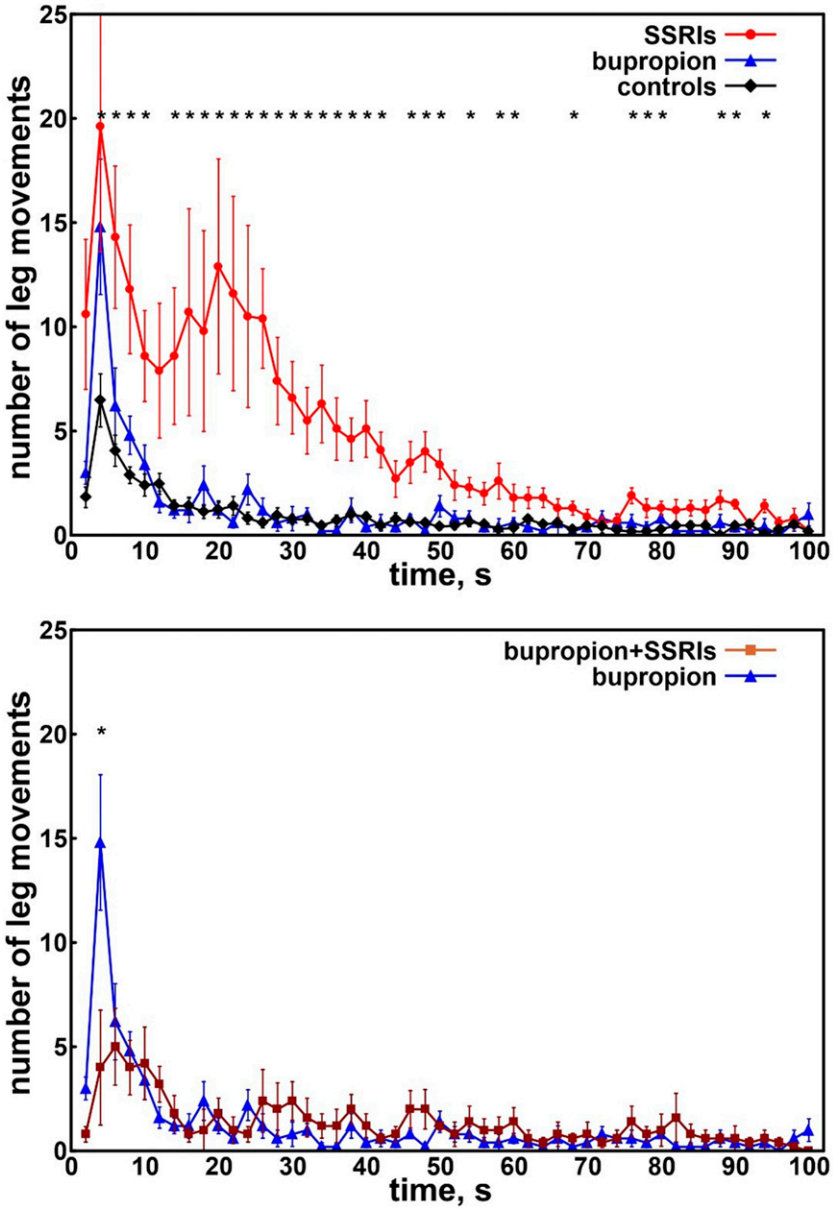
Figure 2 (top panel) displays the number of leg movements recorded during the first 8 hours of sleep in adolescents taking SSRIs or bupropion and in the control patients. A clearly decreasing trend was evident only in adolescents taking SSRIs who also showed values higher than those of the other 2 groups for the entire night, reaching statistical significance during the first 3 hours and during the last hour of sleep. The bottom panel of **Figure 2** reports the distribution of intervals between consecutive leg movements during the first 8 hours of sleep in adolescents taking bupropion alone or those taking bupropion and SSRIs. No significant difference was found in this comparison.

Finally, **Figure 3** shows the atonia index computed during REM sleep and NREM sleep stages in control patients and adolescents taking SSRIs, bupropion alone, or bupropion and SSRIs; the corresponding data are reported in **Table 5**. As expected, the atonia index was highest during REM sleep and lowest during NREM sleep stage N1 in all groups. However, the differences between groups showed a similar pattern within each sleep stage, with the lowest stage values in the 2 groups taking SSRIs and the highest in the control patients. Adolescents taking bupropion alone tended to show values slightly smaller than the control patients; however, most of the between-group comparisons were statistically nonsignificant, most probably because of the insufficient power of this analysis with respect to the effect size found. Only a marginally significant difference was found between the atonia index in sleep stage N2 in patients taking bupropion and SSRIs versus control patients not taking any medication.

DISCUSSION

The main results of this study on a small series of patients taking bupropion, SSRIs, or a combination of both show that SSRIs but not bupropion are associated with increased overall LMS, including not only PLMS but all categories of LMS, such as SILMS and ISOLMS. These results represent a novel finding in the adolescent population, but could be expected, based on the data already available in the literature, especially regarding adults.[9] Definitely novel is our finding of the effectiveness of bupropion to counteract the SSRI-induced increase of PLMS, indicating an inhibitory effect stronger than the facilitatory effect of SSRIs on PLMS and sleep-related leg movements in general. Essentially, the dopaminergic effect of bupropion seems to outmatch the antidopaminergic action of SSRIs, suggesting the possibility to use a combination of these 2 categories of agents when treating mood disorders in adolescents, with the possible added value of a lower risk of other adverse effects along with increased efficacy.[2,4] A study on adults investigated the trend of PLMS in patients treated using SSRIs and using bupropion and a control group, showing an increase in PLMS in the group taking SSRIs and a reduction in PLMS in those taking bupropion and in the control group[17]; however, there seem to be no data in the literature on the effect of bupropion on PLMS in children. The beneficial effect of bupropion on both PLMS, as shown here and previously in adults,[17] and RLS[10] could be hypothesized on the basis of the target areas of the drug (reward system and limbic system, subserved by the mesolimbic dopamine pathway[34]) and their potential involvement in PLMS and RLS; a recent neuroimaging study on patients with RLS and PLMS showed involvement of the subcortical gray structures embedded within the mesolimbic dopaminergic pathway.[35]

Figure 1—Distribution of intervals between consecutive LMS in adolescents.

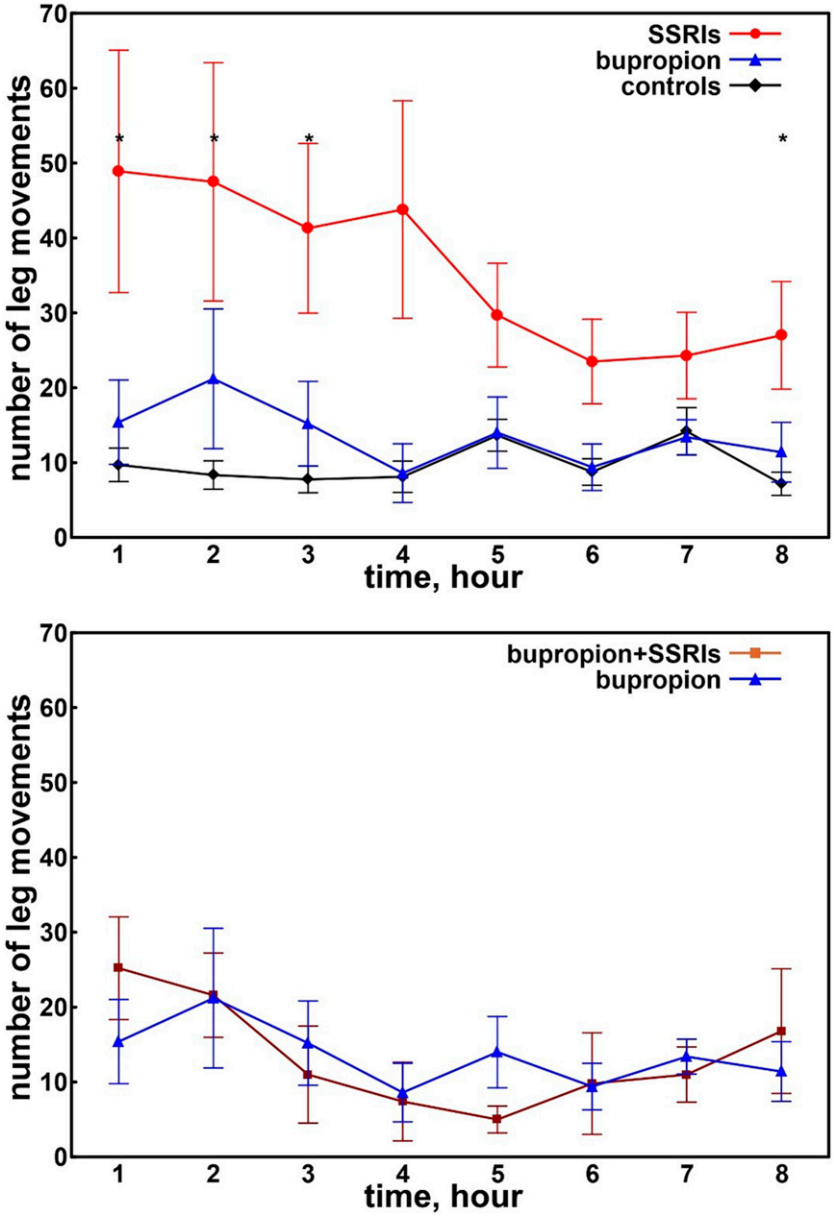


Top panel: Distribution of intervals between consecutive LMS in adolescents taking SSRIs (red circles) or bupropion (blue triangles) and in control patients (black diamonds). Bottom panel: Distribution of intervals between consecutive LMS in adolescents taking bupropion alone (blue triangles) or bupropion plus SSRIs (brown squares). Data are shown as mean and standard errors (whiskers). Asterisks along the top indicate a significant difference ($P < .015$) obtained with the Kruskal–Wallis ANOVA comparing the 3 groups and computed for all points of the graphs. ANOVA = analysis of variance, LMS = leg movements during sleep, SSRIs = selective serotonin reuptake inhibitors.

Very few studies have evaluated the PSG effects of bupropion in adults or children. A study on 19 adult patients taking bupropion showed increased REM sleep latency but no other change in sleep variables.[36] Our study showed a very small prolongation in REM sleep latency in the group of children taking bupropion that did not achieve statistical significance, likely because of the small cohort. Interestingly, this prolongation in REM sleep latency has been correlated with response to treatment in patients with depression.[37]

Bupropion has not been reported to induce or aggravate REM sleep without atonia/REM sleep behavior disorder[38]; however, studies are scarce, and our report indicates the need to deepen our understanding of this aspect and, if confirmed, to clarify the mechanism by which bupropion might affect sleep EMG tone not only during REM sleep. Studies in rodent models have identified the core circuits of REM sleep within the sublaterodorsal tegmental nucleus or subcoeruleus nucleus in humans at the level of the brainstem. Neurons in the sublaterodorsal tegmental nucleus are glutamatergic and control muscle atonia through gamma aminobutyric acid-ergic and glycinergic motor neurons.[39] In agreement with the findings of the current study and those of a previous report,[25] SSRIs can increase

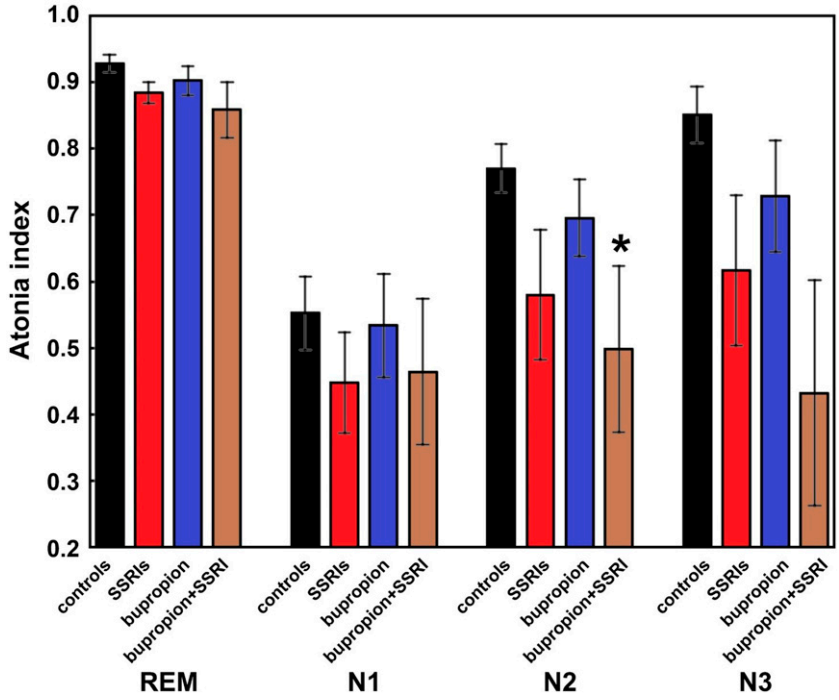
Figure 2—Number of leg movements recorded during the first 8 hours of sleep in adolescents.



Top panel: Number of leg movements recorded during the first 8 hours of sleep in adolescents taking SSRIs (red circles) or bupropion (blue triangles) and in control patients (black diamonds). Bottom panel: Number of leg movements recorded during the first 8 hours of sleep in adolescents taking bupropion alone (blue triangles) or bupropion plus SSRIs (brown squares). Data are shown as mean and standard errors (whiskers). Asterisks on the top indicate a significant difference ($P < .015$) obtained with the Kruskal–Wallis ANOVA comparing the 3 groups and computed for all points of the graphs. ANOVA = analysis of variance, SSRIs = selective serotonin reuptake inhibitors.

serotonin and consequently decrease dopaminergic activity in the descending pathways from the brainstem to the spinal cord motor neurons, not only during REM sleep but also during NREM sleep.[40] Given the apparently different magnitude of the effect of SSRIs and bupropion on muscle tone found in this study and the possible summation of their effects when taken together, we hypothesize that the mechanism by which bupropion might affect muscle tone is different from that of SSRIs. In addition, the lack of bupropion-induced REM sleep behavior disorder in the few reports available may indicate that unlike for LMS, bupropion could not counteract the effects of SSRIs that reduced REM sleep atonia, as expected[22,25]; on the contrary, in this case bupropion seemed to show an effect on the atonia index, slightly reducing it with respect to control patients, and the association of bupropion plus SSRIs produced the lowest values, with a marginally significant difference between the atonia index in sleep stage N2 in patients taking bupropion plus SSRIs and control patients. Some studies suggest a cholinergic modulation of REM sleep atonia circuits[41]; in fact, acetylcholine has pre- and postsynaptic excitatory effects

Figure 3—Atonia index computed during REM sleep and NREM sleep stages.



Atonia index computed during REM and NREM sleep stages in control patients (black-filled columns), adolescents taking SSRIs (red-filled columns), adolescents taking bupropion alone (blue-filled columns), or adolescents taking bupropion plus SSRIs (brown-filled columns). Data are shown as mean (column) and standard errors (whiskers). The asterisk indicates a statistically significant difference versus control patients at $P < .05$ (Mann–Whitney U test). NREM = nonrapid eye movement, REM = rapid eye movement, SSRIs = selective serotonin reuptake inhibitors.

on glutamatergic sublaterodorsal tegmental nucleus neurons that project to the spinal cord.[42] It has been proposed that these cells promote REM sleep atonia, thus suggesting a cholinergic mechanism in the regulation of REM sleep atonia.[43] Bupropion acts on the reward system,[44] with excellent long-term effects, unlike SSRIs[45]; several studies have shown that this action is made possible by its ability to modulate different types of cholinergic receptors[46] and its influence on the nicotinic acetylcholine receptors of neurons from the dorsal raphe nucleus and the hippocampus.[47] The reduction in muscle atonia observed in our study following the intake of bupropion alone could therefore be attributable to the blockade of cholinergic receptors induced by bupropion.

Bupropion is a dopamine and norepinephrine reuptake inhibitor[1]; therefore, our results can be viewed as a further proof of the involvement of the dopaminergic system in PLMS, whose etiopathogenesis, as previously mentioned, is still not completely known.[7,46] In particular, recent neuroimaging studies have evaluated the brain structures on which bupropion acts, giving indications on the mechanisms of action of this drug and therefore indirect indications on the conditions that could benefit from its effects (in this case PLMS). A functional magnetic resonance

Table 5—Atonia index computed during REM sleep and NREM sleep stages in control patients and adolescents taking SSRIs, bupropion alone, or bupropion plus SSRIs.

	Control Patients (n = 17)	SSRIs (n = 10)	Bupropion (n = 6)	Bupropion + SSRIs (n = 6)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
REM sleep atonia index	0.920 (0.890–0.977)	0.882 (0.849–0.901)	0.918 (0.858–0.947)	0.908 (0.780–0.931)
Stage N1 atonia index	0.554 (0.403–0.699)	0.484 (0.244–0.571)	0.588 (0.389–0.692)	0.438 (0.239–0.704)
Stage N2 atonia index	0.792 (0.668–0.883)	0.654 (0.246–0.876)	0.745 (0.593–0.790)	0.463 (0.218–0.732)*
Stage N3 atonia index	0.916 (0.813–0.961)	0.708 (0.494–0.935)	0.746 (0.580–0.935)	0.302 (0.085–0.866)

*Statistically significantly different versus control patients at $P < .05$ (Mann–Whitney U test). IQR = interquartile range, NREM = nonrapid eye movement, REM = rapid eye movement, SSRIs = selective serotonin reuptake inhibitors.

imaging study revealed increased functional connectivity between the dorsal medial prefrontal cortex and posterior cingulate cortex and precuneus in patients receiving bupropion[48]; another study evaluated the degree of neural activation within the reward system, showing reduced activation of the ventral striatum and ventral tegmental area after the administration of paroxetine (an SSRI), but not with bupropion, which instead caused an increase in activation within the sublenticular amygdala.[49] And finally, a recent review evaluated several neuroimaging reports on the effect of bupropion on brain areas, all of which agreed on the involvement of the anterior cingulate cortex and the limbic system.[50]

Our study has also shown that bupropion is not commonly used in the pediatric population, with 14 children taking the medication out of 361 (3.7%) of children on antidepressants undergoing a sleep study. Other therapeutic uses in children and adolescents include ADHD,[1,51] smoking prevention in high-risk children with ADHD,[1,51] smoking cessation therapy in adolescents,[52] conduct disorder,[53] bipolar disorder,[54] and severe morning sleep inertia.[55] It is important to note that ADHD is often associated with RLS and PLMS.[19,20] As evidenced by our study, bupropion did not cause a worsening of PLMS, and it also may counteract the negative effects of SSRIs on them, strengthening the validity of this therapeutic option for the treatment of RLS and PLMS in the presence of ADHD or another comorbidity. Controlled clinical trials would be welcome in this field. It seems that bupropion is an underutilized medication in the pediatric and adolescent population; it has benign[56] and even beneficial effects on sleep, as shown herein, and it does not carry the withdrawal problems that often occur and can be long-lasting with SSRIs/serotonin and noradrenalin reuptake inhibitors that are frequently prescribed.

The main limitation of this study is the small sample size of the groups of adolescents recruited, which was imposed by the retrospective observational nature of the recruitment of participants and by the need to exclude as many confounders as possible, such as the use of additional drugs acting at the level of the central nervous system, in the first place. This important limitation significantly decreased the power of our statistical analysis, which found clearly significant differences only for the parameters involving LMS (with large effect sizes) but not for those related to the chin EMG and the atonia index, in particular, characterized by smaller effect sizes. For this reason, the interpretation of the atonia index results can only be highly speculative and needs to be replicated in larger samples. In any case, a general trend can be noticed that should be considered with great caution; indeed, the lowest stage values were found in the 2 groups taking SSRIs (alone or taken with bupropion) and the highest in the control patients, with adolescents taking bupropion alone who tended to show values slightly smaller than control patients.

In addition to the small sample size, other limitations of this study include the single-center recruitment of patients, the variable dosage and duration of the therapy, and the absence of PSG recordings in the same patients without therapy, before treatment or after a drug wash out.

CONCLUSIONS

Similar to what has been reported in adults,[9,17,57] this study indicates that in adolescents, SSRIs but not bupropion are also associated with increased PLMS. Bupropion also seems to counteract the SSRI-induced increase of PLMS, but not the changes in chin EMG tone,[25,58] when administered in combination with SSRIs; thus, regarding PLMS, the dopaminergic effect of bupropion seems to outmatch the antidopaminergic action of SSRIs whereas it may reinforce that of SSRIs on muscle tone. The results of this study strongly encourage future studies on larger series of patients, from whom important clues can be derived for understanding the underlying mechanisms and treatment. In conclusion, the information provided by our findings represents an important starting point for more powered analyses and controlled studies.

ABBREVIATIONS

ADHD, attention-deficit/hyperactivity disorder
EMG, electromyography
ISOLMS, isolated leg movements during sleep
LMS, leg movements during sleep
NREM, nonrapid eye movement
PLMS, periodic limb movements during sleep
PSG, polysomnography
REM, rapid eye movement
RLS, restless legs syndrome
SILMS, short-interval leg movements during sleep
SSRI, selective serotonin reuptake inhibitor

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