pii: jc-00370-16 http://dx.doi.org/10.5664/jcsm.6462

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content

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Study Objectives: Melatonin is an important neurohormone, which mediates circadian rhythms and the sleep cycle. As such, it is a popular and readily available supplement for the treatment and prevention of sleep-related disorders including insomnia and jet lag. This study quantified melatonin in 30 commercial supplements, comprising different brands and forms and screened supplements for the presence of serotonin.

Methods: A total of 31 supplements were analyzed by ultraperformance liquid chromatography with electrochemical detection for quantification of melatonin and serotonin. Presence of serotonin was confirmed through analysis by ultraperformance liquid chromatography with mass spectrometry detection.

Results: Melatonin content was found to range from −83% to +478% of the labelled content. Additionally, lot-to-lot variable within a particular product varied by as much as 465%. This variability did not appear to be correlated with manufacturer or product type. Furthermore, serotonin (5-hydroxytryptamine), a related indoleamine and controlled substance used in the treatment of several neurological disorders, was identified in eight of the supplements at levels of 1 to 75 µg.

Conclusions: Melatonin content did not meet label within a 10% margin of the label claim in more than 71% of supplements and an additional 26% were found to contain serotonin. It is important that clinicians and patients have confidence in the quality of supplements used in the treatment of sleep disorders. To address this, manufacturers require increased controls to ensure melatonin supplements meet both their label claim, and also are free from contaminants, such as serotonin.

Commentary: A commentary on this article appears in this issue on page 163.

Keywords: contaminant, degradation, label claim, natural health product, stability

Citation: Erland LA, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. *J Clin Sleep Med.* 2017;13(2):275–281.

INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine, produced by the mammalian pineal gland as a neurohormone, but has since been found in almost all clades of life encompassing both vertebrate and invertebrate animals, bacteria, fungi, algae and plants.[1,2] In all kingdoms melatonin is produced from the aromatic amino acid tryptophan. In the mammalian system, biosynthesis then proceeds via hydroxylation to 5-hydroxytryptophan followed by decarboxylation to form serotonin (5-hydroxytryptamine).[3] In the plant system the hydroxylation and decarboxylation steps are reversed and serotonin synthesis proceeds via the metabolic intermediate tryptamine.[4] Though several alternative routes have been identified, the primary biosynthetic pathway for melatonin then proceeds from serotonin to N-acetylserotonin to melatonin and involves addition of a methoxy and N-acetyl group to serotonin.[3–5] The primary role of melatonin in vertebrates is regulation of circadian rhythms, and for humans in particular the sleep cycle, making it a common supplement for the treatment of sleep-related disorders such as insomnia, anxiety, and jet lag.[6–12] Therefore, melatonin is readily available for purchase over the counter from most drugstores and pharmacies, with a diverse selection of formulations available including flavored liquids, rapid-dissolve tablets and strips, traditional liquid gel and solid tablets, and even capsules containing complex mixtures of vitamins, minerals, and whole plant extracts. Because melatonin has been suggested to be unstable under some storage conditions, and melatonin is known to occur naturally in medicinal plants, this raises potential pitfalls that may lead to degradation or modification of the melatonin content in these supplements, especially with such a wide diversity of matrices.[13]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Melatonin is an important neurohormone, which mediates circadian rhythms and the sleep cycle; as such, it is a popular and readily available supplement for the treatment and prevention of sleep-related disorders. As these products are often self-prescribed, it is important that labels are informative and representative of the product, i.e., these products are free from contaminants and label claim values for the active ingredient are accurate.

Study Impact: The products examined in this study showed significant variability of melatonin content as compared to labelled values, and a controlled substance, serotonin, was found in a significant portion of the supplements tested. This raises immediate potential health concerns because consumption of these products is at the consumer's discretion and is often based on label information, highlighting the need for both patient education and comprehensive characterization and standardization of melatonin supplements and the methods of their preparation.

This study, therefore, was designed to determine the actual melatonin content of common over-the-counter melatonin supplements. As a confirmatory measure all melatonin supplements were also screened for the presence of the related indoleamine, serotonin. The results of our analyses of melatonin supplements revealed a significant variation in melatonin content and more interestingly the presence of serotonin in many products.

METHODS

All products investigated in this study were purchased from local grocery stores and pharmacies in Guelph, Ontario. Supplements tested spanned 16 different brands, and included a representative sample of formulations; e.g., liquid, capsule, tablet.

For solid samples, five tablets or capsules were weighed then ground to a fine powder, and the equivalent of one dose was weighed out and extracted. Serotonin and melatonin were extracted from samples in 100% methanol (LC grade, Fisher Scientific, Canada), filtered (0.45 µM, EMD Millipore) and diluted in Milli-Q water to a final melatonin concentration of 1.5 to 5 µg/mL prior to injection (final dilution = 1,000 times for 1.5- to 5-mg samples, final dilution = 2,000 times for 10-mg samples). All samples were prepared in triplicate. Liquid samples were directly diluted and injected.

Samples were run on a Waters Acquity ultraperformance liquid chromatography (UPLC) with an ESA Coulochem III electrochemical detector with a coulometric ultra-analytical cell (Thermo Scientific, USA). For melatonin quantification, 10 µL of sample was run isocratically (25% methanol, 75% 100 mM sodium acetate (Sigma-Aldrich, Canada) and 100 mM citric acid (Sigma- Aldrich, Canada) on a Waters Acquity UPLC HSS T3 column (2.1 × 50 mm, 1.8 µm) with flow rate of 0.4 mL/min, column temperature 35°C and electrochemical detector potentials of 50 mV (screening), and 850 mV (analytical), 1 µA; melatonin eluted at 4 min. For serotonin analysis mobile phase composition was adjusted to 5% methanol, 95% 100 mM sodium acetate with 100 mM citric acid, serotonin eluted at 1.88 min.

Samples were quantified using authentic standards for melatonin (Sigma-Aldrich, Canada) and serotonin (Alfa Aesar, USA). Limit of detection and lower limit of quantification were 0.09 µg/mL and 0.27 µg/mL, respectively, for melatonin and 0.01 µg/mL and 0.03 µg/mL, respectively, for serotonin.

To confirm identity of serotonin in the samples, samples showing presence of serotonin were run on a Waters H-Class Acquity UPLC, with QDa (single quadrupole mass spectrometer, Waters, Canada) detection using the same extraction method as described. A sample (7.5 µL) was injected onto a Waters Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7 µm) and separated using a binary gradient in which mobile phase A was 10 mM ammonium acetate (Sigma-Aldrich), adjusted to pH 9 with ammonium hydroxide (Sigma-Aldrich, Canada), and B was acetonitrile (LC grade, Fisher Scientific, Canada). A 4-min gradient from 95% to 5% A (curve 8) was used to separate components. Flow rate was 0.5 mL/min and column temperature was 40°C. Serotonin was monitored at m/z 177 with a cone voltage of 5. Serotonin eluted at 0.65 min, with a limit of detection of 10 ng/mL.

All data were acquired and processed in Empower software (Waters, Canada).

RESULTS

Melatonin content was found to be highly variable between samples and lots, with no pattern observed between brand, form of supplement, labelled value, or presence of other herbal extracts. The most variable sample, chewable tablet E1, showed a 478% increase from label claim containing almost 9 mg of melatonin, compared to the 1.5-mg label claim, though this was also highly variable between lots (465% difference). The supplement that showed the greatest decrease in melatonin content as compared to labelled values was the capsule G5 which contained lavender, chamomile, and lemon balm, with a decrease of 83%. The least variable products appeared to be those that contained the simplest mix of ingredients, generally tablets or sublingual tablets with melatonin added to a filler such as cellulose derivatives or silica (**Table 1**, **Figure 1**). The capsules generally showed the greatest variability, with the variability observed from E1 greatly distorting the mean results of the chewable category (**Figure 1**). The herbal extracts most commonly added to these capsules included valerian root, passion flower, chamomile, skullcap, and hops, though other extracts were also found in some supplements (**Table 1**). Surprisingly, lot-to-lot variability was as varied as deviation from the label claim, ranging from 0.37% up to 466% (**Table 1**, **Figure 2**), with little correlation with other descriptive factors, though again, the sublingual tablets and tablets were most reproducible. Liquid supplements, though suspected to be the least stable, due to melatonin's known instability at room temperature in solvent, were generally high to medium in their stability (**Figure 1**) with low lot-to-lot variability (**Figure 2**).

Serotonin was found in 8 of the 30 samples tested (**Table 2**). These results were confirmed by MS in all cases with the exception of Q1 for which serotonin was found only by electrochemical detection, though this could be attributed to long storage of this particular sample after extraction because limited doses were available for this product. Of these, the majority were supplements that contained other herbal supplements or extracts such as passionflower, hops, and valerian root as was the case for G5, G3, C1, J1, R1, S1, and N2, whereas the remaining supplement (E1) was a chewable tablet with 5-hydroxytryptophan and L-theanine added. Serotonin content ranged from as low as 1.21 µg/mL in supplement R1 to as high as 74.27 µg/mL in G5. In all cases where two lots were available, serotonin was found in both, and lot-to- lot variability was similar to or lower than what was observed for melatonin content in the respective supplements with differences ranging from 1.25% up to 133%.

DISCUSSION

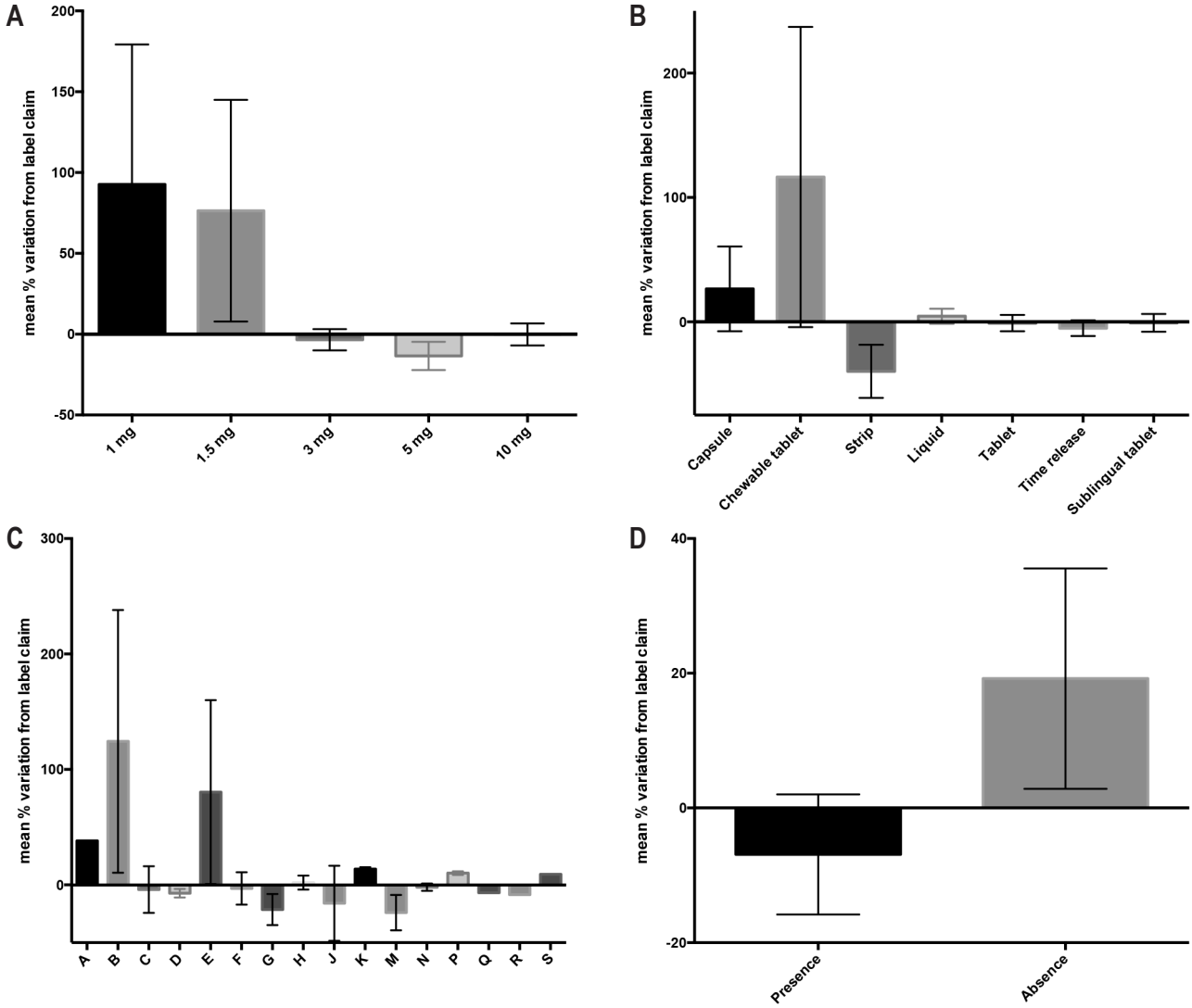
The results of melatonin content across brands, supplement type, and lot demonstrates significant variability from label claim.

Table 1—Summary of melatonin content in supplements tested.

Product code	Lot	Form	Label claim, mg	Melatonin present, mg/unit (standard error)	Difference from label claim, mg	Difference from label claim, %	Difference between lots, %	Other medicinal ingredients or extracts [a]
A-1	1	Capsule	3	4.14 (0.242)	1.14	38.1		
B-1	1	Liquid	3	3.37 (0.035)	0.37	12.2	3.28	
	2		3	3.27 (0.077)	0.27	8.9		
B-2	1	Capsule	1	4.52 (3.326)	3.52	351.8		
C-1	1	Tablet	1.5	1.23 (0.023)	−0.27	−18.3	28.58	Chinese skullcap, passion flower, lemon balm, valerian, hops
	2		1.5	1.65 (0.044)	0.15	10.3		
D-1	1	Sublingual tablet	5	5.11 (0.059)	0.11	2.2		
D-2	1	Chewable tablet	1.5	1.31 (0.024)	−0.19	−12.9	1.10	L-theanine, 5-HTP
	2		1.5	1.32 (0.056)	−0.18	−11.8		
D-3	1	Timed- release tablet	5	5.08 (0.128)	0.08	1.7	16.86	
	2		5	4.24 (0.145)	−0.76	−15.2		
E-1	1	Chewable tablet	1.5	8.67 (0.074)	7.17	478.1	465.44	L-theanine, 5-HTP
	2		1.5	1.31 (0.015)	0.19	12.7		
E-2	1	Sublingual tablet	5	5.14 (0.039)	0.14	2.9	9.08	
	2		5	4.69 (0.239)	−0.31	−6.2		
E-3	1	Timed- release tablet	10	9.18 (0.304)	−0.82	−8.2	11.30	
	2		10	10.31 (0.346)	0.31	3.1		
F-1	1	Sublingual tablet	3	3.62 (0.074)	0.62	20.6	1.58	
	2		3	3.57 (0.271)	0.57	19.1		
F-2	1	Soft gel	5	2.44 (0.085)	−2.56	−51.3		
F-3	1	Liquid	10	11.46 (0.299)	1.46	14.6	33.01	
	2		10	8.16 (0.325)	−1.84	−18.4		
G-1	1	Sublingual tablet	5	1.44 (0.140)	−3.56	−71.2	83.93	
	2		5	5.64 (0.041)	0.64	12.7		
G-2	1	Sublingual tablet	3	3.38 (0.032)	0.38	12.7		
G-3	1	Capsule	3	3.35 (0.099)	0.35	11.7		Hops, chamomile, valerian, passionflower, spirulina
G-4	1	Fast- dissolving strips	3	1.16 (0.582)	−1.84	−61.3	42.84	
	2		3	2.45 (0.078)	−0.55	−18.4		
G-5	1	Capsule	3	0.53 (0.086)	−2.47	−82.5	103.31	Lavender, chamomile, lemon balm
	2		3	3.63 (0.087)	0.63	20.8		
G-6	1	Timed- release tablet	10	8.38 (0.147)	−1.62	−16.2		
H-1	1	Tablet	3	3.24 (0.037)	0.24	8.0	12.05	
	2		3	2.88 (0.235)	−0.12	−4.1		
J-1	1	Capsule	1.5	1.75 (0.075)	0.25	16.6	64.97	Valerian, passionflower, lemon balm, GABA, L-theanine, 5-HTP
	2		3	1.55 (0.075)	−1.45	−48.4		
K-1	1	Spray	1	1.12 (0.039)	0.12	12.1	3.18	
	2		1	1.15 (0.040)	0.15	15.3		
M-1	1	Sublingual tablet	5	3.03 (1.517)	−1.97	−39.4	30.70	
	2		5	4.57 (0.196)	−0.43	−8.7		
N-1	1	Sublingual tablet	3	2.98 (0.090)	−0.02	−0.8	4.52	
	2		3	2.84 (0.047)	−0.16	−5.4		
N-2	1	Capsule	3	2.75 (0.029)	−0.25	−8.2	14.65	Valerian, hops, passionflower, chamomile
	2		3	3.19 (0.084)	0.19	6.5		
P-1	1	Sublingual tablet	5	6.23 (0.191)	1.23	24.6	0.37	
	2		10	12.50 (0.873)	2.50	25.0		
P-2	1	Liquid	10	7.28 (0.058)	−2.72	−27.2	45.73	
	2		10	11.85 (0.174)	1.85	18.5		
Q-1	1	Capsule	3	2.80 (0.026)	−0.20	−6.8		Passionflower
R-1	1	Capsule	1	0.91 (0.019)	−0.09	−8.5		Methylsulfonylmethane (MSM), chamomile, passion flower, skullcap, valerian
S-1	1	Slow- release tablet	3	3.28 (0.091)	0.28	9.2		

[a] Hops (*Humulus lupulus*), Chinese skullcap (*Scutellaria bicalensis*), passionflower (*Passiflora incarnate/incarnate*), lemon balm (*Melissa officinalis*), valerian (*Valeriana officinalis*), chamomile (*Matricaria recutita*), lavender (*Lavandula angustiolifa*).

Figure 1—Mean percent variability across melatonin supplements.

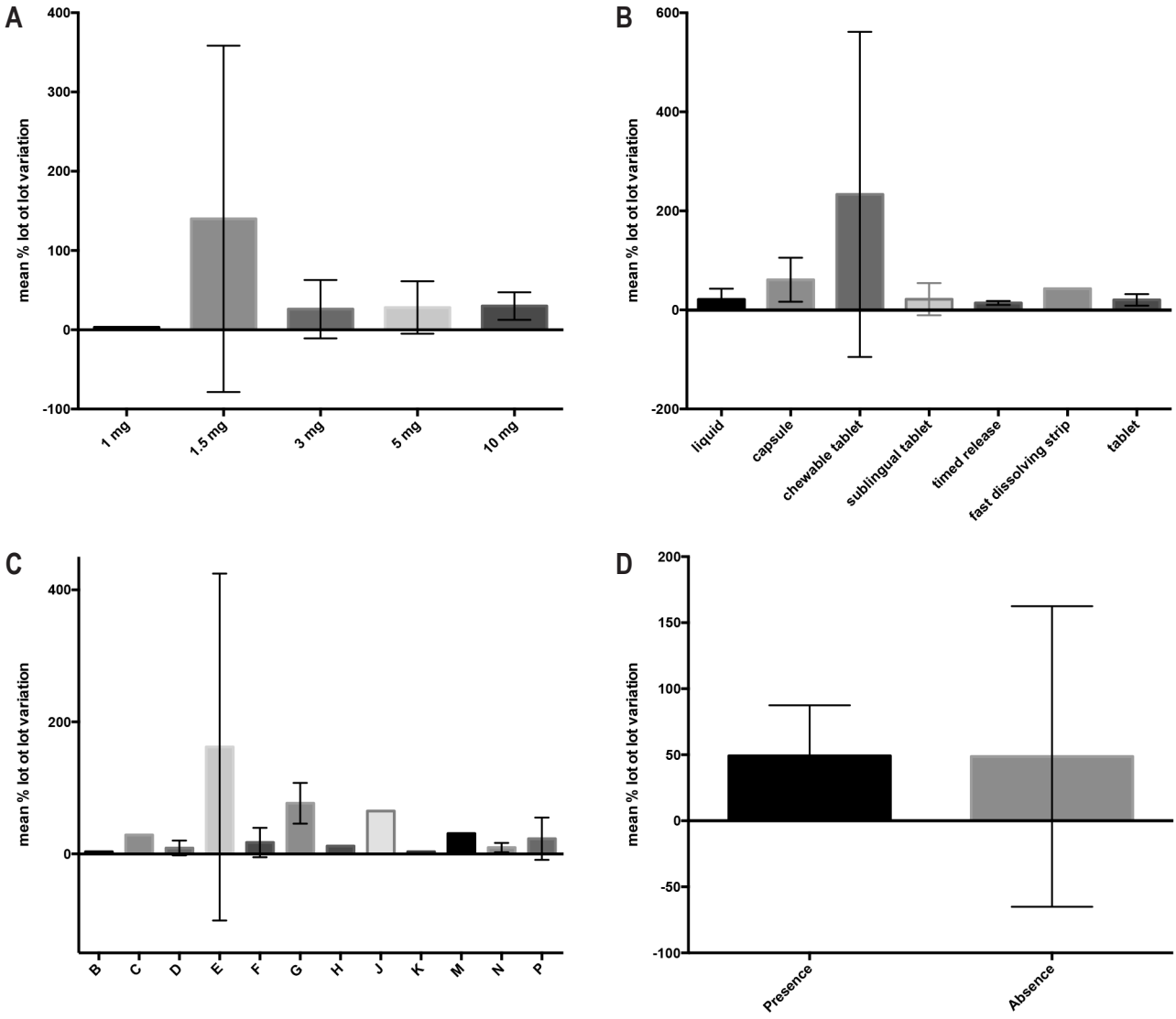


Grouped by **(A)** label claim value, **(B)** supplement type, **(C)** brand, and **(D)** presence or absence of other plant extracts. Error bars represent standard error margin.

Though a decrease in actual melatonin content as compared to label claim was expected because of degradation or stability issues, the number of products with a significant increase in melatonin content was not anticipated. These excessive values may be explained by intentional addition of excessive melatonin to ensure that products meet label claim, assuming label claim as a minimum value compared to actual value. Though this is unlikely to present a significant health concern, evidence suggests that higher doses of melatonin could lead to unpleasant or unexpected side effects in some patients. This includes persons who are more sensitive to exogenous melatonin treatment, those who are taking medications that may show drug interactions with melatonin, or those who have particular medical conditions such as diabetes or prediabetes or who are pregnant.[12]

Serotonin is a biosynthetic precursor of melatonin and a potent neurotransmitter, whose levels are correlated to many processes and disease states including neurological disorders such as drug addiction, depression, and migraines.[14–16] Though early steps in the melatonin biosynthetic pathway vary between organisms, serotonin is known to be a required precursor in all organisms, and as such has been found in as diverse of clades as melatonin.[1,5,17] Serotonin is, however, a much more strictly controlled substance and cannot be purchased in supplement form. In fact, it would in most circumstances be an undesirable contaminant, as serotonin overdose can be achieved with relatively low levels and can lead to serious side effects, which in extreme cases can be fatal.[18,19] Because the majority of melatonin found in the supplements tested is either sourced from porcine pineal gland or more frequently produced synthetically, it seemed unlikely that serotonin will be found in these supplements. Although the presence of serotonin in supplements containing other herbal extracts such as passionflower or chamomile could be attributed to natural phytoserotonin from these plant extracts, the presence of serotonin in those supplements lacking these extracts is more difficult to explain. This is not necessarily indicative of contamination in the

Figure 2—Mean percent variability between melatonin supplement lots.



Grouped by **(A)** label claim value, **(B)** supplement type, **(C)** brand, and **(D)** presence or absence of other plant extracts. Error bars represent standard error margin.

manufacturing process, particularly as the degradation products of melatonin are as yet poorly understood both in chemical formulations and plant tissues. The presence of unlabelled but significant quantities of serotonin in melatonin supplements is of particular concern, as these types of supplements are poorly controlled, often self-prescribed, and could easily lead to an accidental overdose. It is therefore important to identify the source of this contaminant serotonin.

A 2010 Ipsos-Reid survey commissioned by Health Canada estimated that 73% of Canadians use natural health products.[20] Melatonin is used widely by the public as an over-the-counter supplement in the management of sleep disorders including insomnia and jet lag.[6–8,10] Though melatonin consumption is generally considered to be of little risk, there have been reports of interaction of melatonin with other botanical and medicinal products, as well as negative side effects if taken in excess in the short term.[21–25] In contrast with melatonin, serotonin has much more significant health concerns if taken in excess, leading to a condition known as serotonin syndrome, which ranges from very mild to fatal in its outcome, which can be exacerbated by interactions with other medications, such as selective serotonin reuptake inhibitors (SSRIs) and the analgesic tramadol.[18,19,26,27] The large discrepancy in melatonin content compared to label claim and the presence of serotonin in a large percentage of supplements indicates that current best practices for production of melatonin supplements may require further attention, and further emphasizes that natural over-the-counter supplements do not always equal zero-risk alternatives to traditional medications.

CONCLUSIONS

Our results demonstrate a high variability, ranging from −83% to +478% of the labelled concentration of melatonin content in

Table 2—Summary of serotonin content in supplements in which it was detected.

Product code	Lot	Serotonin present, µg	Standard error, µg	Absolute % difference between lots
C-1	1	7.422	0.689	1.25
	2	7.33	0.496	
E-1	1	6.462	1.028	60.90
	2	12.12	0.349	
G-3	1	2.9	0.252	
G-5	1	74.27	12.94	22.40
	2	59.31	1.274	
J-1	1	36.86	0.929	113.64
	2	10.15	0.724	
N-2	1	5.158	0.404	15.26
	2	6.01	0.552	
Q-1	1	3.73	0.614	
R-1	1	1.21	0.372	

melatonin supplements. In addition, the related indoleamine, serotonin, was also found in 8 of the 30 melatonin supplements tested. The presence of serotonin in melatonin supplements is likely to open further questions on biosynthesis and degradation of these important compounds and related potential health concerns. These results emphasize the need for further research to determine the best manufacturing procedures and mechanisms to monitor melatonin content in the products to ensure consistency and safety of the supplements.

ABBREVIATIONS

LLOQ, lower limit of quantification
LOD, limit of detection
UPLC, ultra performance liquid chromatography

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2016
Submitted in final revised form October, 2016
Accepted for publication October, 2016
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DISCLOSURE STATEMENT

This work was supported by the National Sciences and Engineering Research Council (NSERC) of Canada grant number 46741. The authors have indicated no financial conflicts of interest.