Improvement in daytime sleepiness with clarithromycin in patients with GABA-related hypersomnia: Clinical experience

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Short Report

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Abstract

The macrolide antibiotic clarithromycin can enhance central nervous system excitability, possibly by antagonism of GABA-A receptors. Enhancement of GABA signaling has recently been demonstrated in a significant proportion of patients with central nervous system hypersomnias, so we sought to determine whether clarithromycin might provide symptomatic benefit in these patients. We performed a retrospective review of all patients treated with clarithromycin for hypersomnia, in whom cerebrospinal fluid enhanced GABA-A receptor activity *in vitro* in excess of controls, excluding those with hypocretin deficiency or definite cataplexy. Subjective reports of benefit and objective measures of psychomotor vigilance were collected to assess clarithromycin's effects. Clinical and demographic characteristics were compared in responders and non-responders. In total, 53 patients (38 women, mean age 35.2 (SD 12.8 years)) were prescribed clarithromycin. Of these, 34 (64%) reported improvement in daytime sleepiness, while 10 (19%) did not tolerate its side effects, and nine (17%) found it tolerable but without symptomatic benefit. In those who reported subjective benefit, objective corroboration of improved vigilance was evident on the psychomotor vigilance task. Twenty patients (38%) elected to continue clarithromycin therapy. Clarithromycin responders were significantly younger than non-responders. Clarithromycin may be useful in the treatment of hypersomnia associated with enhancement of GABA-A receptor function. Further evaluation of this novel therapy is needed.

Keywords

Clarithromycin, hypersomnia, GABA-A, idiopathic hypersomnia, narcolepsy, excessive daytime sleepiness

Introduction

The central nervous system hypersomnias are disorders that result in substantial excessive daytime sleepiness despite adequate quality and quantity of nocturnal sleep, and include the entities of idiopathic hypersomnia and narcolepsy. Recent work has demonstrated a presumptive small peptide in cerebrospinal fluid (CSF) of many of these subjects that enhances GABA-A receptor function *in vitro* (Rye et al., 2012). Because of GABA's central role in promoting sleep and diminished states of consciousness (Franks, 2008; Lu and Greco, 2006; Posner et al., 2007), such bioactivity has the potential to cause pathological sleepiness. Preliminary evidence for causality derives from observations that the GABA-A receptor antagonist flumazenil normalizes vigilance metrics in patients with hypersomnia associated with abnormal potentiation of GABA-receptors (Rye et al., 2012). However, because flumazenil is formulated and approved only for intravenous use, it presently may be an impractical choice for the treatment of chronic hypersomnia conditions. Oral agents that act as negative allosteric modulators or antagonists of the GABA-A receptor might be an alternative therapeutic approach.

While using a proprietary combination of sublingual and transdermal flumazenil (Rye et al., 2012), a patient with primary hypersomnia and excessive enhancement of GABA-A receptor function was serendipitously prescribed the macrolide antibiotic clarithromycin by her internist to treat acute bronchitis. On this combination therapy, a period of severe insomnia lasting several days ensued which resolved upon discontinuation of clarithromycin. Clarithromycin is known to have neurotoxic adverse effects, which typically manifest as central nervous system excitation, including insomnia, mania, psychosis, and non-convulsive status epilepticus (Abouesh et al., 2002; Bandettini di Poggio et al., 2011; Wallace et al., 1993), although sleepiness has less often been reported (Baranowski, 2011). The mechanism of action of this neurotoxicity remains unknown, although direct neurotoxicity, hormonal dysregulation (especially of cortisol or prostaglandins), or effects on hepatic metabolism of other drugs have all been proposed (Bandettini di Poggio et al., 2011). Although effects on GABA transmission have also been hypothesized to underlie such adverse events with clarithromycin (Lopes et al., 2011), only recently has clarithromycin's effects as an antagonist of GABA been demonstrated *in vitro* (Garcia and Jenkins, 2009). Given that sleepiness in many of our patients with hypersomnia

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has been refractory to conventional psychostimulants and wake-promoting strategies (Rye et al., 2012), we were compelled to begin clinical use of clarithromycin in patients with hypersomnia. Here, we present a retrospective review of our clinical experience with clarithromycin use in all treated patients to date with a central nervous system hypersomnia, and whose spinal fluid potentiated GABA-A receptor function *in vitro*.

Methods and materials

We identified all central nervous system hypersomnia patients whose CSF had been shown to enhance GABA-A receptor function in an *in vitro* electrophysiologic assay (Rye et al., 2012). In this assay, whole-cell patch-clamp recording is used to measure the potentiation of GABA-A receptor currents in human embryonic kidney cells (HEK293) transfected to express wild-type human α1, β2, and γ2 subunits of the GABA-A receptor. Inhibitory chloride currents are significantly potentiated when cells are exposed to 10μM GABA combined with CSF from patients with hypersomnia, compared with the CSF from non-sleepy controls (Rye et al., 2012). From the group of hypersomnia patients demonstrating levels of enhancement greater than controls on this assay, we selected all those who had taken oral clarithromycin from September 2008 through November 2012. All patients met DSM-IV criteria for narcolepsy or primary hypersomnia (including Kleine–Levin syndrome). Because patients with hypocretin-deficient narcolepsy were not included in the initial work identifying abnormal GABA-A receptor signaling in hypersomnia patients (Rye et al., 2012), we did not include patients with unambiguous cataplexy or documented CSF hypocretin levels < 110 pg/mL.

We collected information regarding patient impressions of clarithromycin therapy from the electronic medical record, including assessment of effectiveness as well as any reported adverse events. We routinely assess vigilance in hypersomnolent patients during outpatient visits and multiple sleep latency tests using the psychomotor vigilance task (PVT) (Dinges, 1985), and when available, we compared PVT performance in individual subjects while on and off clarithromycin. Because clarithromycin non-responders and those with intolerable side effects were typically not taking clarithromycin at follow-up, PVT data analyses were limited to those who reported subjective improvement with therapy. As an exploratory analysis, clinical and demographic variables between subjective responders and subjective non-responders were compared using *t*-tests for continuous variables and chi-square for categorical variables. In cases of categorical variables where expected cell counts would be less than 5, Fisher's exact test was used instead of chi-square. This study was approved by our institutional review board.

Results

Some 53 patients took clarithromycin and provided feedback about their response. An additional six patients were prescribed clarithromycin but had not yet returned for follow-up. Of the patients, 38 (72%) were women. Mean age was 35.2 years (standard deviation (SD) 12.8 years). Diagnoses of the 53 included patients were primary hypersomnia ($n = 41$, of whom two had Kleine–Levin syndrome) and narcolepsy without cataplexy ($n = 12$). The 53 patients had failed an average of 2.6 (SD 1.4) wake-promoting medications, either because of lack of efficacy or intolerable side effects, before being prescribed clarithromycin.

Clarithromycin was typically prescribed as 500 mg to be taken orally with breakfast and lunch for a 2-week trial period. Depending on the preference of the prescribing physician, some patients were instructed to increase the dose to 1000 mg with breakfast and lunch if the lower dose did not sufficiently alleviate excessive daytime sleepiness after 3–4 days; others did not exceed a total daily dose of 1000 mg regardless of effectiveness. Clarithromycin was typically added to the patients' existing medication regimen ($n = 34$, 66.7%) and less often used as monotherapy ($n = 17$, 33.3%); in two patients, the order of usage was ambiguous. Among the 53 patients, mean daily dose was 1098 mg (SD 371 mg). Patients who reported symptom improvement with treatment during the 2-week trial period were considered for long-term clarithromycin use.

Of the 53 treated patients, 34 (64%) reported improvement in daytime sleepiness (Figure 1). Ten patients (19%) did not tolerate clarithromycin because of side effects, which included gastrointestinal distress ($n = 5$), bad taste ($n = 2$), headache ($n = 1$), feeling weak and tremulous ($n = 1$), a sensation of panic ($n = 1$), worsened sleep quality ($n = 1$), and unspecified intolerance ($n = 1$; two patients experienced more than one side effect). Eight patients tolerated the medication for a 2-week trial period but experienced no improvement in their sleepiness. One patient was reassessed after taking therapy for only a single day and did not note any benefit, for a total of nine non-responders (17%).

Of the 34 patients who reported subjective benefit during the initial 2-week trial period, 23 (68%) chose to continue taking clarithromycin on a long-term basis, at an average total daily dose of 1102 mg (SD 275 mg). Of these, 16 continued to take clarithromycin on a daily basis, four patients continued to take clarithromycin on an as-needed basis, and three patients took clarithromycin for an average of 5 months before discontinuing therapy (one for gastrointestinal side effects, one because a loss of efficacy, and one for a combination of factors including cost and variability in medication effectiveness). Among the 16 patients actively using clarithromycin on a chronic, daily basis, the average duration of use was 8.7 months (SD 6.8 months, range 1–22 months) at the time of last clinical follow-up. Of the remaining 11 initial treatment responders, four were prescribed long-term therapy but had not yet returned for clinical follow-up, two patients felt their prior therapy was preferable to clarithromycin (flumazenil plus modafinil in one case, protriptyline in one case), two patients preferred to try other therapies before deciding on which medication to use for the long term, two patients reported that their subjective benefit was outweighed by unpleasant side effects, and one patient did not fill her prescription because of medication cost.

Among the patients who reported subjective improvement with clarithromycin, PVT data with and without clarithromycin use were available for 18 patients (53%). Median reaction time was significantly improved with clarithromycin (253.6 ms, SD 55.4 ms, on clarithromycin vs. 305.8, SD 116.0 ms, without clarithromycin, $p = 0.014$), as was the reciprocal reaction time of the slowest 10% of responses (2.84, SD 0.66, on clarithromycin versus 2.27, SD 0.63, off clarithromycin, where higher numbers are indicative of faster reaction times, $p = 0.0005$). The number

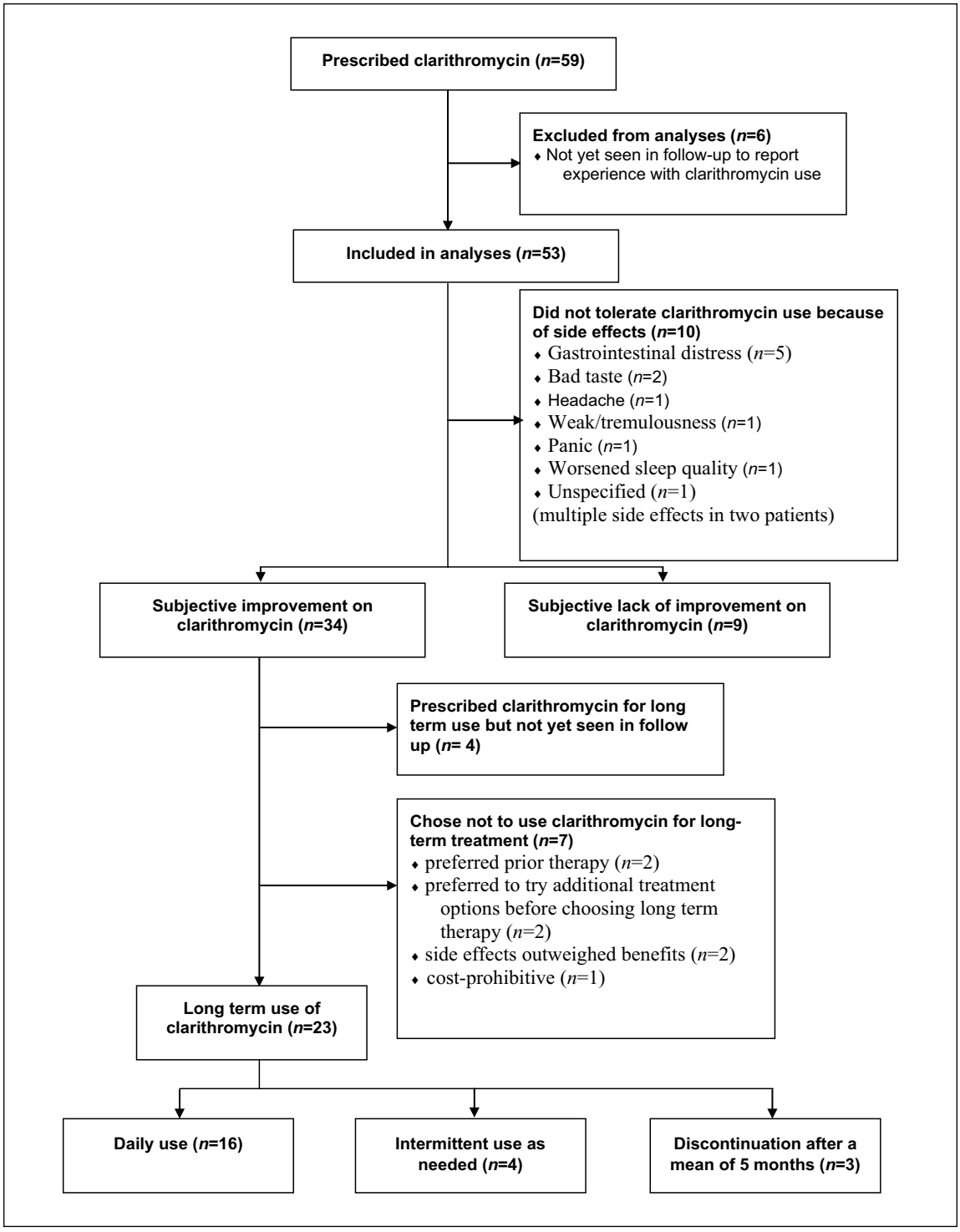

Figure 1. Summary of patient experience with clinical use of clarithromycin.

of attentional lapses (i.e. reaction times > 500 ms) was not significantly different (2.7, SD 6.1, on clarithromycin vs. 7.7, SD 15.1, off clarithromycin, $p = 0.06$).

Compared with those patients who did not note subjective improvement from clarithromycin, patients who reported improvement were significantly younger (Table 1). Mean daily dose of clarithromycin was higher in the nine patients who did not respond, as expected given that some patients were instructed to increase the dose if they found that the initial 500 mg twice daily dose did not improve sleepiness. There were no other significant differences between responders and non-responders.

Table 1. Characteristics of included subjects.

	Entire group (n = 53)	Clarithromycin responders (n = 34)	Clarithromycin non-responders (n = 9)	p-value
Age (in years)	35.2 (12.8)	32.6 (12.0)	45.2 (10.7)	**0.007**
Diagnosis	Primary hypersomnia: 41 (77%) Narcolepsy: 12(23%)	Primary hypersomnia: 29 (85%) Narcolepsy: 5 (15%)	Primary hypersomnia: 6 (66%) Narcolepsy: 3 (33%)	0.33
Female gender	38 (72%)	26 (76%)	4 (44%)	0.10
Body mass index	26.0 (5.4)	25.7 (5.8)	28.2 (4.8)	0.25
Habitual weekly sleep duration in hours	67.5 (13.8)	69.8 (12.7)	64.0 (12.0)	0.24
Epworth Sleepiness Scale score prior to clarithromycin	16.0 (3.6)	15.6 (4.0)	17.7 (2.2)	0.16
Number of wake-promoting medications failed prior to using clarithromycin	2.6 (1.4)	2.6 (1.4)	3.1 (1.5)	0.30
History of depression	23 (43.4%)	13 (38.2%)	5 (55.6%)	0.46
Mean percent potentiation at GABA-A receptor*	86.0 (28.2)	88.4 (30.8)	95.2 (23.3)	0.54
Sleep efficiency on PSG (expressed as a percentage)	88.1 (9.8)	88.8 (7.8)	82.6 (12.5)	0.13
Total sleep time on PSG (in minutes)	384.9 (56.6)	375.8 (49.2)	386.9 (88.0)	0.78
Mean sleep latency on MSLT (in minutes)	7.0 (4.8)	8.0 (5.3)	4.9 (3.1)	0.17
Number of sleep onset REM periods on MSLT	1.0 (1.4)	0.86 (1.1)	0.83 (2.0)	0.97
Clarithromycin daily dose (in mg)	1097.8 (370.7)	1016.1 (295.3)	1500.0 (534.5)	**0.04**
Number of patients using clarithromycin as monotherapy during initial trial period	17 (33.3%)	11 (33.3%)	3 (37.5%)	1.0

Values are presented as mean (SD) or number (percentage), as appropriate. p-values reflect t-test, chi-square test, or Fisher's exact test. Patients who had side effects that prevented them from completing a 2-week course of clarithromycin are included in column 2 but not columns 3 or 4. PSG: polysomnography; MSLT: multiple sleep latency test; REM: rapid eye movement. *as described in Rye et al. (2012) (average reported value for non-sleepy controls 35.8 (SD 7.5)).

Discussion

Nearly two-thirds of the patients with primary hypersomnia or narcolepsy without cataplexy, all of whom demonstrated CSF evidence for abnormal GABA-A receptor activity, reported subjective improvement in sleepiness during a short-term course of clarithromycin. Among patients with subjective improvements in sleepiness, significant improvements in PVT-measured vigilance were also observed. Some 38% of patients initially prescribed a short-term course of clarithromycin continued to use it chronically for management of their daytime sleepiness.

There are no FDA-approved treatments for primary or idiopathic hypersomnia. Typically, these patients are treated with medications approved for narcolepsy, despite the lack of clinical trial evidence supporting their use (Morgenthaler et al., 2007). While some patient series have documented good response among patients with hypersomnia to current standard-of-care treatments such as modafinil (Lavault et al., 2011), others have emphasized that clinical response may be incomplete in one-third of patients (Ali et al., 2009; Anderson et al., 2007; Wise et al., 2007). The patients included in our series had inadequate control of their hypersomnia symptoms despite having previously tried an average of 2.6 other wake-promoting medications prior to choosing clarithromycin therapy. This group thus represents a medication-refractory subgroup of hypersomnia patients, in whom novel and effective treatment options are needed.

Side effects during short-term clarithromycin use were problematic in 19% of patients, and affected long-term treatment choice in an additional 13%. Long-term use of clarithromycin has the potential for additional side effects that were not observed in our patients, including antibiotic resistance and super-infection. Thus, any benefit from clarithromycin will need to convincingly outweigh these risks to justify its continued use. Long-term clarithromycin use has been recommended or considered for a variety of other conditions in which a similar risk/benefit calculus suggests that its chronic use may be warranted, including non-tuberculous mycobacterial diseases, (Griffith et al., 2007), rhinosinusitis (Luo et al., 2011; Zeng et al., 2011), and cystic fibrosis (Dogru et al., 2009; Nakamura et al., 2013; Robinson et al., 2012). However, these conditions have an infectious etiology or are worsened by superimposed infection, whereas hypersomnia is not presumed to be related to bacterial infection. Therefore, the use of clarithromycin for hypersomnia requires consideration of the principle of antibiotic stewardship. As expressed by the Infectious Disease Society of America, this principle is, "to optimize clinical outcomes while minimizing the unintended consequences of antimicrobial use" (Dellit et al., 2007). While inherent in this principle is the idea that the risk of using the medication (i.e. an increase in antibiotic resistance) must be appropriately balanced by benefit, the use of antibiotics for non-infectious etiologies is not explicitly excluded as long as clinical outcomes justify use. If additional studies confirm the benefit of clarithromycin for hypersomnia symptoms, such treatment would be consistent with this principle. Chronic use of clarithromycin for other non-infectious conditions, for example multiple myeloma, is also currently being evaluated (Gay et al., 2010; Morris et al., 2008).

In patients with cardiovascular disease, there might be an increased risk of cardiovascular mortality associated with short-term use of clarithromycin or other antibiotics (Gluud et al., 2008; Jespersen et al., 2006; Winkel et al., 2011), but this remains

a controversial topic and has not been shown consistently across multiple investigations (Andersen et al., 2010; Andraws et al., 2005; Cercek, 2008). The most recent safety warning from the United States Food and Drug Administration (FDA) regarding clarithromycin includes a risk of arrhythmias, but does not note an increased risk of death in patients with cardiovascular disease despite acknowledging the results of the Jespersen study (US Food and Drug Administration, 2005, 2012).

Another possible complication of long-term clarithromycin use might be the development of tolerance or need for dose escalation. Clarithromycin's actions at the GABA-A receptor might increase this risk, as with other medications with GABA-A receptor targets (Uusi-Oukari and Korpi, 2010). In our series, one patient discontinued chronic therapy because of loss of efficacy (after successful use for 9 months) and one patient discontinued chronic therapy due to a combination of variable effectiveness over time and insurance reasons. Two of the intermittent users reported choosing this dosing strategy because of variable efficacy over time. Thus, some degree of tolerance is likely present, but the true rate requires further study. Finally, clarithromycin is metabolized by and is an inhibitor of the cytochrome P450 3A subfamily. As a result, drug interactions with other medications metabolized by this subfamily are possible and may preclude clarithromycin use in patients on such medications.

Mechanistically, the actions of clarithromycin as an antagonist of the GABA-A receptor (Garcia and Jenkins, 2009) are the most parsimonious explanation for its benefit on excessive sleepiness in hypersomnia syndromes associated with an excess potentiation of action of the GABA-A receptor. However, alternative mechanisms of action are also possible. For example, clarithromycin decreases *in vitro* production of cytokines that are known to be soporific (Clinton et al., 2011; Morikawa et al., 1996), which could translate into decreased sleepiness with clarithromycin use. Alternatively, changes to gastrointestinal flora with clarithromycin use could affect sleepiness. Eradication of *Helicobacter pylori* infection with clarithromycin has been suggested to decrease encephalopathy by decreasing ammonia levels (Agrawal et al., 2011; Chen et al., 2008). Although speculative, an analogous decrease in levels of ammonia, or other bacterial by-products, could theoretically be at work in patients with hypersomnia treated with clarithromycin.

The current study was a retrospective review of clinical experience, and therefore was limited by available data within the medical record. Our clinic is a tertiary-referral centre for patients with hypersomnia, which may bias our population toward those with treatment-refractory hypersomnia symptoms and potentially limits the applicability of these findings to the larger population of hypersomnia patients. However, based on these preliminary findings, clarithromycin appears to be a potentially useful and novel treatment option in patients with central nervous system hypersomnia whose CSF is documented to exhibit abnormal potentiation of the GABA-A receptor. Important questions about clarithromycin use for the treatment of hypersomnia remain, including demonstration of efficacy in a randomized controlled trial, more rigorous evaluation of long-term safety, and comprehensive assessment of its tolerance potential. However, given the treatment-refractory nature of sleepiness that is persistent and troublesome in about one-third of hypersomnia patients (Ali et al., 2009; Anderson et al., 2007), the use of clarithromycin in selected patients should be considered.

Conflict of interest

Dr. Trotti has consulted for UCB Pharma. Dr. Bliwise is a consultant for Ferring and the New England Research Institute. Drs. Jenkins and Rye are co-inventors on a pending patent (US 20110028418A1) for the use of flumazenil to treat hypersomnia. Dr. Rye is a consultant for UCB Pharma and Jazz Pharmaceuticals. For the remaining authors, no conflicts of interest were declared.

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