Efficacy and Tolerability of Tadalafil, a Novel Phosphodiesterase 5 Inhibitor, in Treatment of Erectile Dysfunction

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Advances in molecular biology and protein chemistry, along with increasing understanding of the mechanisms of penile erection, have spurred development of pharmacologic approaches to the treatment of erectile dysfunction (ED). The next generation of oral agents includes tadalafil, a potent, highly selective phosphodiesterase 5 inhibitor. In vitro studies have shown that tadalafil enhances relaxation of trabecular smooth muscle, and clinical trials have supported its efficacy and tolerability in a broad population of men with ED. The effect of tadalafil in enhancing the erectile response to sexual stimulation is relatively rapid in onset and lasts for ≥24 hours. The ability of patients with ED treated with tadalafil to achieve improved erectile function is demonstrated by significantly increased subjective measures of penetration ability, successful intercourse, and sexual satisfaction. Partners have expressed similar or higher levels of satisfaction with the results of treatment. Men with ED of psychogenic, organic, or mixed etiology and in a range from mild to severe have experienced significant improvment with tadalafil treatment. Response to treatment in men with diabetes has been robust and not affected by disease severity. Tadalafil has been well tolerated. Adverse events have generally been mild or moderate and have abated with continued treatment. Headache and dyspepsia have been most frequently reported. Changes in color vision have been rare (<0.1%) with tadalafil across all clinical trials. Tadalafil appears to be a safe and effective treatment for men with ED. ©2003 by Excerpta Medica, Inc.

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The era of oral treatment for erectile dysfunction (ED) began in 1976 with the identification in lung tissue of a phosphodiesterase (PDE) specific to cyclic guanosine monophosphate (cGMP), as reviewed by Corbin and Francis.[1] The advent of oral treatment, however, awaited advances in molecular biology and protein chemistry, as well as insight into the neurovascular mechanisms of the erectile response.

A key 1989 study by Sáenz de Tejada et al[2] found that neural and endothelium-dependent mechanisms that would normally cause relaxation in corporal smooth muscle were impaired in tissue collected from men with diabetes and ED. This evidence led the investigators to conclude that decreased synthesis or release of an endothelium-dependent relaxing factor was responsible.[2] This factor has since been identified as nitric oxide.

Nitric oxide is now known to be the principal mediator of smooth muscle relaxation in the corpus cavernosum.[3] Released from nerve endings and endothelial cells on sexual stimulation, nitric oxide triggers an intracellular cascade that leads to erection. Nitric oxide activates the cytosolic enzyme guanylate (also termed guanylyl) cyclase in smooth muscle cells, increasing the generation of cGMP. A specific protein kinase (protein kinase G) is, in turn, activated with ensuing phosphorylation events. The end result is a decrease in cytosolic calcium levels and relaxation of smooth muscle.[4,5]

Elucidation of the nitric oxide–cGMP pathway identified PDE5, which inactivates cGMP. It was reasoned that inhibiting PDE5 would prolong the effects of nerve stimulation, and considerable therapeutic interest was directed to drugs with inhibitory capacity. Although early PDE5 inhibitors were developed for cardiac conditions and allergic asthma, it became apparent that these drugs might be effective treatments for ED.[6] The selective PDE5 inhibitor sildenafil was introduced in 1996, and the next generation of PDE5 inhibitors includes tadalafil (Cialis; Lilly ICOS LLC Bothell, WA, and Indianapolis, IN), which is under investigation for the treatment of ED.

Orally administered, tadalafil is a potent, highly selective, reversible inhibitor of PDE5. Pharmacokinetic studies in healthy volunteers have shown that tadalafil is rapidly absorbed, with the maximum plasma concentration occurring at 2.0 hours, and that it has an elimination half-life of 17.5 hours.[7] Clinical response to tadalafil, which may be evident as early as 16 minutes after an oral dose, persists for ≥24 hours.[8,9] The absorption of tadalafil is unaffected by age, the presence of diabetes or mild-to-moderate hepatic insufficiency, or food intake.[10] In clinical trials to date, tadalafil has shown evidence of both broad efficacy and tolerability.[11,12]

TADALAFIL SPECIFICITY AND EFFECT ON TRABECULAR SMOOTH MUSCLE

The selectivity profile of tadalafil was evaluated against 14 human recombinant PDEs, including PDE6

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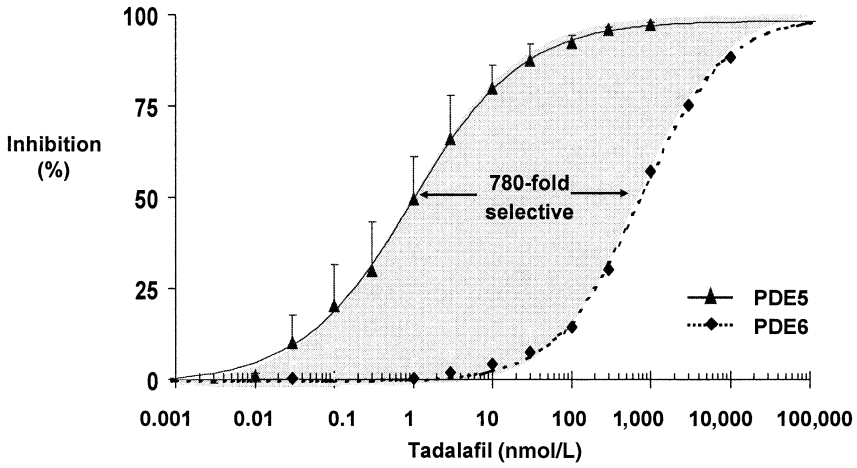

FIGURE 1. Tadalafil inhibition of human phosphodiesterase 5 (PDE5) and 6 (PDE6) isoenzymes. Compared with PDE5, a 780-fold greater concentration of tadalafil is needed to inhibit PDE6. Error bars indicate standard deviation. (Adapted from *Eur Urol.*[5])

obtained from human retinas.[5] Tadalafil was found to be highly selective for PDE5, with an approximately 700-fold greater affinity for PDE5 than for the related retinal enzyme PDE6.[13] Compared with inhibition of PDE5, a 780-fold greater concentration of tadalafil was needed to inhibit PDE6 (Figure 1) in a study by Angulo et al.[5] A >10,000-fold concentration of tadalafil is needed to inhibit the activity of all the other recombinant PDE isoforms tested (PDE1 to PDE4 and PDE7 to PDE10) compared with PDE5.[13] Tadalafil has exhibited a 14-fold greater affinity for PDE5 compared with PDE11, a newly identified isoenzyme that is widely distributed throughout the body and whose clinical significance is unknown.

To evaluate the effect of tadalafil on smooth muscle relaxation in human penile resistance arteries and trabecular smooth muscle, Angulo et al[5] collected corpora cavernosa tissues from patients with ED during penile prosthesis implantation surgery. The tadalafil formulation significantly increased the neurogenic relaxant effects of acetylcholine and sodium nitroprusside on human trabecular smooth muscle. This finding suggests that tadalafil potentiates the relaxant effect of nitric oxide, whichever the route of production: acetylcholine induces release of nitric oxide, leading to endothelium-dependent vasodilation, whereas sodium nitroprusside acts directly on vascular smooth muscle to stimulate guanylate cyclase.[14] Taken together, these in vitro findings indicate that tadalafil is highly selective for PDE5 and improves penile erection in patients with ED by augmenting the nitric oxide–cGMP pathway.

EFFICACY OF TADALAFIL

The following trials of tadalafil summarize clinical experience to date in various populations of men with ED. Eligibility criteria for all trials included ED of ≥3 months' duration and a stable relationship with a female partner. All trials were randomized, double blind, and placebo controlled. All but 1 study (of time to onset of response) was multicenter. Except for a pilot study—which assessed erectile response to tadalafil with a RigiScan (Timm Medical Technologies, Eden Prairie, MN), a penile plethysmography device—efficacy outcome measures have been evaluated using a validated, self-administered recall instrument and at-home diary (Table 1).[8]

The International Index of Erectile Function (IIEF) is a validated, 15-item, self-administered questionnaire that comprises 5 relevant domains of sexual function: (1) erectile function, (2) orgasmic function, (3) sexual desire, (4) intercourse satisfaction, and (5) overall sexual satisfaction.[15] Extensively tested and validated (and used worldwide), the IIEF is a sensitive and specific instrument for detecting treatment-related changes (Table 1).[15]

Sexual Encounter Profile (SEP) diaries consist of a series of yes/no questions (6 for the patient, 4 for his partner) specific to each sexual encounter (Table 1). Two global assessment questions (GAQs), administered after the treatment period, assess whether treatment improved patients' erections (GAQ-1) and their ability to engage in sexual activity (GAQ-2) (Table 1). For all trials that took place at home, baseline IIEF and SEP data were obtained at a pretreatment clinic visit.

Duration of response: The duration of response to tadalafil was assessed in a crossover study of 61 men aged 18 to 65 years, each of whom received both tadalafil 10 mg and placebo.[8] The study comprised 2 sequential treatment periods, separated by 7 to 14 days. Each treatment period included 2 test sessions with RigiScan evaluation: a 60-minute session with visual sexual stimulation immediately after administration of a single study dose, and a 30-minute session 24 hours after administration of the dose.[8] Response was defined as ≥55% penile rigidity for ≥3 consecutive minutes. Extreme responders (those achieving high rigidity over prolonged periods during the screening) were excluded from the study; these were

TABLE 1 Subjective Assessments for Efficacy Outcome Measures

Global Assessment Questions
- Q1. Has the treatment you have been taking over the past study interval improved your erections? [yes/no]
- Q2. [If yes] Has the treatment improved your ability to engage in sexual activity? [yes/no]

Sexual Encounter Profile
- Q. Did you attempt to have a sexual encounter? [yes/no] If yes:
- Q1. Were you able to achieve at least some erection? [yes/no]
- Q2. Were you able to insert your penis into your partner's vagina? [yes/no]
- Q3. Did your erection last long enough for you to complete intercourse with ejaculation? Or, Did your erection last long enough to have successful sexual intercourse? [yes/no]
- Q4. Were you satisfied with the hardness of your erection? [yes/no]
- Q5. Were you satisfied overall with this sexual experience? [yes/no]

International Index of Erectile Function Domains
Erectile Function Domain
- Q1. Over the past 4 weeks, how often were you able to get an erection during sexual activity? (scored 1–5)
- Q2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration? (scored 1–5)
- Q3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? (scored 0–5)
- Q4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? (scored 0–5)
- Q5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? (scored 1–5)
- Q15. Over the past 4 weeks, how do you rate your confidence that you can get and keep an erection? (scored 1–5)

Overall Satisfaction Domain (scored 0–10)
- Q13. Over the past 4 weeks, how satisfied have you been with your overall sex life?
- Q14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

Intercourse Satisfaction Domain (scored 1–15)
- Q6. Over the past 4 weeks, how many times have you attempted sexual intercourse?
- Q7. Over the past 4 weeks, when you attempted sexual intercourse, how often was it satisfactory for you?
- Q8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?

men with rigidity at the base of the penis for ≥3 minutes. Also excluded were men who were unable to achieve ≥20% rigidity for ≥3 minutes during an initial 30-minute RigiScan session.[8]

Compared with placebo, tadalafil 10 mg significantly increased the proportion of patients able to achieve an erection at 24 hours after dose (Figure 2) and the cumulative mean time of ≥55% penile rigidity at 24 hours after dose (both, $p = 0.001$). The difference in response between tadalafil 10 mg and placebo was statistically significant 45 minutes after the dose was administered ($p < 0.05$). Approximately 1 hour after tadalafil 10-mg dosing, the plasma tadalafil concentration was 113 μg/L, which decreased to 69 μg/L 24 hours later. At both plasma concentrations, tadalafil was superior to placebo in producing an erectile response.[8]

Time to onset of response: A 3-arm study evaluated time to response in 223 patients randomly assigned to 1 of 3 groups: (1) tadalafil 10 mg, (2) tadalafil 20 mg, or (3) placebo. Exclusion criteria included a history of alcohol abuse, glycosylated hemoglobin values >13%, hypertension, or hypotension. Patients (≥21 years old) received a total of 4 doses of study medication and were instructed to take 1 dose every 8 to 10 days when ready to engage in sexual activity.[8]

After each dose, the earliest time to an erection enabling vaginal penetration and successful intercourse was measured with a stopwatch. Although patients were not specifically instructed to make additional sexual attempts during the first 24 hours after dose, such attempts were also recorded in SEP diaries if they occurred.[8]

Response was defined as ≥1 erection sufficient for successful intercourse within 30 minutes after dose over the course of the study. The earliest time that tadalafil was statistically superior to placebo in reaching this end point was 16 minutes after a 20-mg dose ($p = 0.012$). At 30 minutes, 52% of men taking tadalafil 20 mg and 38% of men taking tadalafil 10 mg were considered responders. Among the responders, tadalafil 20 mg resulted in an erection within 30 minutes 80% of the time, within 25 minutes 61% of the time, and within 20 minutes 47% of the time.

Daily tadalafil in a dose-ranging study: Among the earliest clinical trials of tadalafil was a European study of the safety and effectiveness of daily doses up to 100 mg in men with mild-to-moderate ED.[16] Doses of the study drug (10, 25, 50, or 100 mg) or placebo were randomly assigned to 294 men (mean age, 52.4 years), who took the test dose daily for 3 weeks. All doses significantly increased, over placebo, the ability to penetrate the partner (IIEF–question [Q]3) and to maintain an erection after penetration (IIEF-Q4). Scores for every IIEF domain in each active-treatment group were significantly increased (improved) over placebo ($p \leq 0.001$). Figure 3 shows results on the IIEF erectile function domain.[16]

Based on SEP diary scores, the proportions of both successful intercourse attempts and satisfying intercourse attempts were significantly increased over placebo for both patient and partner ($p \leq 0.001$).[16]

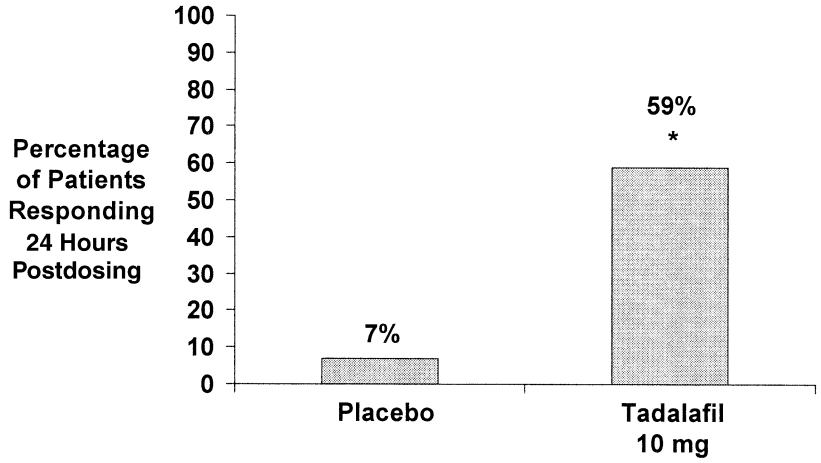

FIGURE 2. Proportions of patients able to achieve an erection 24 hours after administration of tadalafil 10 mg or placebo. Response is defined as having an erection with ≥55% rigidity for ≥3 minutes. *p = 0.001 vs placebo. (Adapted from *J Urol.*[8] Reprinted from *Eur Urol Suppl 1*, Porst H. Restoring a normal sexual response: the ultimate goal of erectile dysfunction therapy, 19–24. Copyright (2002), with permission from the European Association of Urology.)

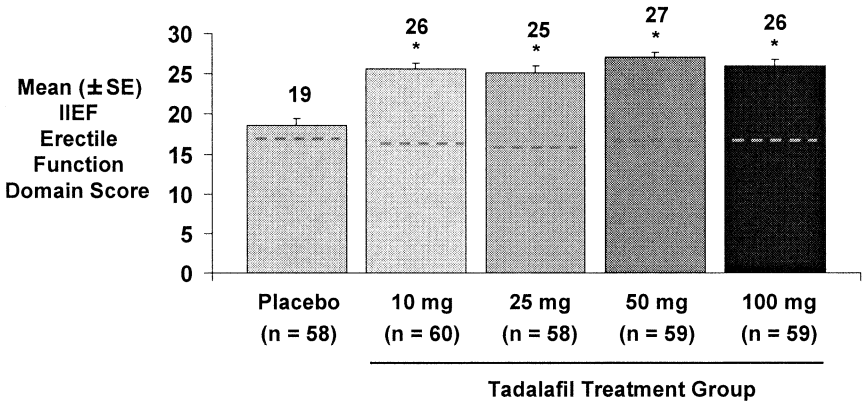

FIGURE 3. Effects of tadalafil treatment (10, 25, 50, 100 mg) compared with placebo on the International Index of Erectile Function (IIEF) erectile function domain score (the sum of IIEF questions 1 through 5, plus 15). *p ≤0.001 vs placebo, based on comparison of the least-square means. *Dashed lines* indicate mean baseline scores. (Adapted from *Eur Urol.*[16])

These results compare well with previously published proportions of successful and satisfying intercourse attempts that range up to 93% with PDE5 inhibitor treatment. Patients receiving tadalafil reported, in a range from 81% to 90%, that the study drug improved erections (GAQ-1). In contrast, 38% of the placebo group reported improved erections ($p \leq 0.001$).[16]

As-needed tadalafil for a broad range of ED: From April 1999 to April 2001, 5 randomized, double-blind, placebo-controlled, parallel-group trials were conducted at 74 centers in eligible patients (n = 1,112) with mild-to-severe ED.[12] These patients were randomly allocated to receive oral placebo (n = 308) or tadalafil at doses of 2.5 mg (n = 74), 5 mg (n = 151), 10 mg (n = 321), or 20 mg (n = 258) at a maximum frequency of once daily for ≥12 weeks. Patients were instructed to take tadalafil as needed anytime before intercourse, without restrictions on food intake or the timing of sexual activity. A broad range of patients was eligible for randomization, with the exception of those taking nitrates, having unstable cardiovascular disease, or exhibiting other conditions unsuitable for sexual activity.[12] Patients could participate regardless of prior treatment with sildenafil citrate or the therapeutic outcome of such therapy.

The IIEF, SEP diaries, and a GAQ were used to evaluate erectile function. Both the IIEF and SEP diaries were collected at baseline and at each 4-week visit. At the final visit, patients were asked, "Has the treatment you have been taking improved your erections?" (GAQ-1 with yes/no response).[12]

The 5 treatment arms (placebo and tadalafil 2.5, 5, 10, and 20 mg) were well matched in baseline characteristics. Patients ranged in age from 22 to 82 (mean, 59) years, and most (approximately 90% in all treatment arms) had ED durations of >1 year.[12] In 59% of patients, ED was moderate or severe according to scores on the erectile function domain of the IIEF,[17] and the predominant etiology based on clinical judgment was organic

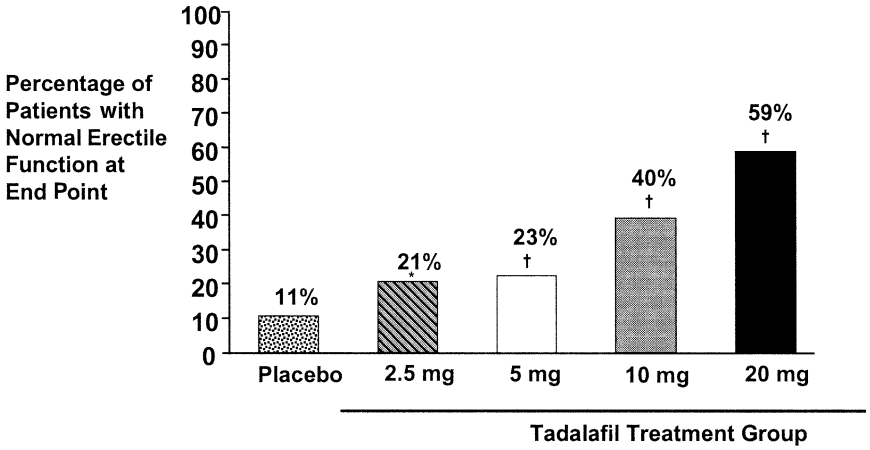

FIGURE 4. Proportions of tadalafil-treated (2.5, 5, 10, 20 mg) patients (vs placebo controls) with normal erectile function[17] at end point. Normal erectile function is defined as International Index of Erectile Function (IIEF) erectile function domain score ≥26. *p <0.05 for tadalafil 2.5 mg vs placebo; †p <0.001 for tadalafil 5, 10, and 20 mg vs placebo. (Reprinted with permission from *J Urol*.[12])

(60.5%). A total of 235 men (21%) had diabetes mellitus, 329 (30%) had hypertension, 86 (8%) had coronary artery disease, and 57 (5%) had depression.[12]

Treatment with tadalafil significantly enhanced erectile function (compared with placebo) across all 3 co-primary efficacy outcome variables. Patients randomized to as-needed tadalafil at all doses had significantly greater ($p < 0.001$) improvements from baseline in the erectile function domain of the IIEF, with end point scores of 21.1 and 23.9 in the tadalafil 10-mg and 20-mg groups, respectively, compared with 15.1 in placebo controls.[12]

The IIEF erectile function domain score observed in the tadalafil 20-mg treatment arm approached the threshold value associated with "no ED."[17] As shown in Figure 4, erectile function returned to normal in 59% of patients randomized to tadalafil 20 mg and 40% of patients randomized to tadalafil 10 mg, compared with 11% of controls ($p < 0.001$).[12] Within each baseline ED severity category, tadalafil 5 to 20 mg significantly augmented mean IIEF erectile function domain scores compared with placebo, and responses to tadalafil 20 mg were consistently greater than responses to tadalafil 10 mg (Figure 5).[12]

Tadalafil taken as needed at each dose also significantly increased (from baseline) the likelihood of vaginal penetration (SEP-Q2) and intercourse completion (SEP-Q3) compared with placebo. At study end point, 61% and 75% of sexual encounters resulted in successful intercourse among men treated with tadalafil 10 and 20 mg, respectively, compared with 32% in controls ($p < 0.001$ for each comparison; Figure 6).[12]

In addition to these significant improvements, tadalafil treatment also enhanced erectile function according to the GAQs. Of men randomized to tadalafil, 81% taking tadalafil 20 mg and 67% taking tadalafil 10 mg reported that treatment improved their erections, as against 35% with placebo ($p < 0.001$).[12]

Compared with placebo controls, men who received as-needed tadalafil exhibited significant improvements from baseline to end point in both IIEF erectile function domain scores and percentages of attempts leading to successful intercourse regardless of baseline age (≥65 or <65 years), diabetes status, or ED severity.[12]

Efficacy in a population with diabetes: A phase 3 trial of tadalafil focused on men with diabetes mellitus (type 1 or 2) with or without retinopathy and with mild-to-severe ED. Men whose diabetes was uncontrolled, however, were excluded. After a 4-week run-in period, 216 patients (mean age, 55.7 years) were randomly assigned to 1 of 3 treatment arms (tadalafil 10 mg, tadalafil 20 mg, or placebo) to be taken for 12 weeks.[18]

Scores on the IIEF erectile function domain increased (improved) significantly from baseline in both active-treatment groups compared with placebo controls ($p < 0.001$). For this domain, the proportion of patients whose scores increased >5 points over baseline (considered a clinically significant response) was greater in the tadalafil 20-mg treatment group than in the tadalafil 10-mg group.[18] Improvement in erectile function with tadalafil 10 or 20 mg was unrelated to diabetes type, current diabetes therapy, initial level of glycemic control, or presence of microvascular complications. Compared with placebo, both 10- and 20-mg tadalafil doses significantly improved ($p < 0.001$) penetration ability and the ability to maintain erection during intercourse, as assessed by IIEF-Q3 and IIEF-Q4, respectively. Scores on both the IIEF intercourse satisfaction domain and overall satisfaction domain were significantly higher in patients treated with tadalafil 10 mg or tadalafil 20 mg compared with placebo.[18] Both 10- and 20-mg doses of tadalafil were also superior to placebo in improving the propor-

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