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A Review of Transdermal Hormonal Contraception

Focus on the Ethinylestradiol/Norelgestromin Contraceptive Patch

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Abstract

Imperfect use of contraceptive methods notably increases the likelihood of pregnancy. One means of improving user adherence with hormonal contraception is to minimize the dosing schedule. Two forms of hormonal contraceptive have currently achieved this goal: the transdermal patch and the vaginal ring. The first and only transdermal contraceptive patch to receive worldwide regulatory approval (ethinylestradiol/norelgestromin) is a convenient approach to contraception that has a similar efficacy to oral contraceptives (OCs), but with the benefit of once-weekly administration. In addition, transdermal delivery of contraceptive hormones eliminates variability in gastrointestinal absorption, avoids hepatic first-pass metabolism, and prevents the peaks and troughs in serum concentrations that are seen with OCs. Norelgestromin, the progestin contained in the patch, is the active metabolite of norgestimate and is structurally related to 19-nortestosterone. Norgestimate and norelgestromin mimic the physiologic effects of progesterone at the progesterone receptor; however, norelgestromin has negligible direct or indirect androgenic activity, suggesting that it may be suitable for women with disorders related to androgen excess (such as hirsutism, acne, and lipid disorders).

Contraceptive effectiveness is usually a function of the efficacy of a contraceptive in combination with compliance with its dosing regimen. The efficacy of the contraceptive patch has been clearly demonstrated in three phase III trials, two of which were randomized comparisons with an OC. The likelihood of pregnancy was similar between these contraceptive methods; however, compliance with the patch was notably better, particularly in younger women. The safety and tolerability profile of the patch was similar to that of the OC. A

cost-effectiveness analysis has suggested that the contraceptive patch is more cost effective than the OC, due to decreased costs related to unwanted pregnancy.

Although the oral contraceptive (OC) pill is a highly effective method of birth control used by millions of women worldwide, imperfect compliance with the once-daily dosing regimen notably increases the risk of pregnancy.[1,2] One means of improving adherence with contraception is to decrease user dependence by minimizing the dosing schedule.[3] This has been achieved with the development of the contraceptive vaginal ring and the transdermal contraceptive patch. Vaginal ring technology and contraceptive effectiveness have been reviewed previously[4,5] and are outside the scope of this review. The first and only transdermal contraceptive patch to receive worldwide regulatory approval (ethinylestradiol/norelgestromin [0.6mg/6mg]; Evra™)[1] is a convenient and pragmatic approach to hormonal contraceptive delivery that provides similar efficacy to the OC, with the benefit of once-weekly administration. Phase III clinical studies in >3300 women (examining 22 155 cycles) have demonstrated that the contraceptive patch is able to suppress ovulation and is effective at preventing pregnancy,[6-8] with an adverse effect profile similar to that seen with OCs.[9]

This review describes the utility of a transdermal drug delivery system, outlines the biologic and clinical actions of norelgestromin, and discusses the contribution of the transdermal contraceptive patch to pertinent issues in contraception. As the norelgestromin/ethinylestradiol patch is the only contraceptive patch currently available, the review of clinical data is focused on this product. However, new transdermal contraceptive patches containing levonorgestrol/ethinylestradiol and ethinylestradiol/gestodene, which are currently in late-phase development, will add further options for physicians in the near future. The first section of this review is a description and analysis of patch technology, providing a brief pharmacologic overview of this new technology in the hormonal contraceptive field. The second section reviews the contraceptive profile of the transdermal patch containing ethinylestradiol/norelgestromin.

1. Patch Technology for Contraceptive Delivery

1.1 Development of Patch Technology

Transdermal drug delivery systems represent >80 years of intensive investigation and have been successfully developed for a number of drugs across a range of therapeutic areas.[10] As such, patch technology represents a convenient method of continuous drug delivery.

The fundamental challenge to transdermal drug penetration is crossing the barrier of the skin, which has a low permeability to foreign molecules owing to the lipid-rich composition of the stratum corneum.[10] Solutes passing through the skin must move between cells and along the interfaces of extracellular lipid bilayers. Because of this, sophisticated pharmacologic and technical approaches are required to allow continuous drug delivery through the skin. The transdermally delivered drug must exhibit the appropriate physical properties to facilitate passage (such as a low molecular mass, high lipophilicity, and high potency) and, together with any adjuvant, must not generate an immune reaction within the skin. From a technical perspective, the actual patch must be able to deliver the drug in a constant manner, adhere appropriately to the skin, and be cosmetically acceptable.

The ethinylestradiol/norelgestromin contraceptive patch is a 20cm^2 matrix patch that contains a total drug content of ethinylestradiol 0.6mg and norelgestromin 6.0mg (17-deacetyl norgestimate, the active metabolite of norgestimate), and delivers a daily dose of ethinylestradiol 20μg and norelgestromin 150μg over the 7 days that it is worn.[11] The patch is composed of three layers: a backing polyester layer, a drug adhesive middle layer, and a release liner that is removed before application. It can be applied to the buttock, abdomen, upper outer arm, or upper torso and should be changed every 7 days for 3 weeks, with a patch-free week at the end of each cycle.

1.2 Clinical Advantages of a Transdermal System for Contraception

Using a transdermal system for contraception presents a number of clinical advantages over conventional OCs. The once-weekly administration is more convenient for women than once-daily administration with OCs and should also improve efficacy by decreasing the degree to which it is dependent on user compliance. However, unlike other some other long-acting contraceptive delivery systems, such as depot progestin, subdermal progestin implants, or intrauterine progestin devices, patch-delivered contraception can be easily withdrawn if necessary.

From a pharmacokinetic perspective, transdermal delivery of contraceptive hormones eliminates variability in gastrointestinal (GI) absorption, due to factors such as stomach pH, stomach

1 The use of trade names is for product identification purposes only and does not imply endorsement.

emptying rate, GI motility, and GI transit time. The drug is delivered directly into the systemic circulation, avoiding the hepatic first-pass metabolism experienced with OCs and maintaining constant drug concentrations in the circulation by eliminating the peaks and troughs in serum progestin and estradiol concentrations that occur with oral administration.

2. Biologic Effects of Norelgestromin

A range of synthetic progestins are used in combination hormonal contraceptives and these affect ovulation and cycle control. These can be classified into those derived from (i) 17-acetoxy progesterone (e.g. medroxyprogesterone acetate and megestrol acetate); (ii) 19-nortestosterone (e.g. norethindrone, lynestrenol, desogestrel, levonorgestrel, and norgestimate); and (iii) 17-α-spironolactone (e.g. drospirenone).[12] Over recent years, there has been a growing realization of the inherent differences in progestins in terms of their pharmacokinetic, biologic, and androgenic properties.[12,13]

Norelgestromin (17-diacetyl norgestimate) is the active metabolite of norgestimate, a synthetic progestin that is structurally related to 19-nortestosterone (specifically, to the 18-ethylgonane subgroup), and is used in several monophasic and triphasic OC formulations. Norgestimate and norelgestromin may be considered equivalent from metabolic and endocrine perspectives.[14] Norgestimate is rapidly hydrolyzed in the liver to norelgestromin by cleavage of an acetyl group, with norelgestromin concentrations in the circulation greatly exceeding those of norgestimate. Norelgestromin bears most of the progestogenic properties of norgestimate. The pharmacologic effects of the other metabolites of norgestimate remain to be fully elucidated.[14]

2.1 Pharmacokinetics of Norelgestromin

The pharmacokinetics of the progestins, including the rates of absorption, hepatic metabolism, and tissue distribution and clearance, vary considerably depending on the route of administration.[12,13,15]

Following oral administration of a single dose of norgestimate, maximum concentrations of norelgestromin are achieved at 1.5 hours, with a half-life that exceeds 24 hours.[14] The pharmacokinetics of norelgestromin administered transdermally have also been evaluated.[16] In a single-dose study, 18 women wore the contraceptive patch on their abdomen for 7 days. Serum concentrations of norelgestromin were maintained within the therapeutic reference range (0.6–1.2 ng/mL) for the entire 7-day period without the peaks and troughs characteristic of OCs. Furthermore, when the duration of patch application was extended to 10 days (a 3-day dosing error) in a subsequent study, serum concentrations remained within the reference range. When patches were worn for 3 weeks (changed every 7 days), steady state concentrations of 0.70–0.80 ng/mL were achieved, with minimal accumulation of norelgestromin over time. Varying the patch application site and climatic conditions did not significantly alter the concentration-time profile of norelgestromin. Moreover, daily serum concentrations of norelgestromin and ethinylestradiol were within the ranges generally seen with orally administered ethinylestradiol/norgestimate 35μg/250μg.

2.2 Biologic Actions of Norelgestromin

The modulating effect of progestins depends on the potential interaction with five different types of receptor, including the progesterone receptor (A and B isoforms), the androgen receptor, the estrogen receptor, the glucocorticoid receptor, and the mineralocorticoid receptor.[13,15] Progestins may also competitively bind to sex hormone-binding globulin with low or high affinity, and progesterone (but not any of the progestins) has been shown to bind to corticosteroid-binding globulin.[15] The desired pharmacologic properties of a synthetic progestin used for contraception are progestational activity with a lack of androgenic activity. A displacement study in rat uterine tissue suggested that the relative binding affinity of norgestimate for the progesterone receptor was 24% greater than progesterone itself.[17] In another study, the relative binding affinity for norgestimate at the progesterone receptor was 15% relative to promegestone (progesterone affinity relative to promegestone was 50%), with no affinity for the other receptors described (aside from a 1% affinity for the glucocorticoid receptor relative to dexamethasone).[15]

The negligible binding affinities of norgestimate for the androgen receptor and sex hormone-binding globulin[15,17] reflect the low androgenicity of this progestin, which is a desirable property in a contraceptive. In a clinical study using the contraceptive patch or a norgestimate-containing OC, key androgenic markers were reduced in healthy volunteers,[18] suggesting that a norgestimate or norelgestromin-containing contraceptive may improve disorders of androgen excess. These include hirsutism, acne, and lipid disorders. Acne is related to androgen excess in skin tissue. Inhibition of 5α-reductase (responsible for transforming testosterone to the more potent 5α-testosterone) in the skin has implications for the treatment of acne.[19] *In vitro* studies have demonstrated that norgestimate is a highly potent inhibitor of 5α-reductase in skin tissue, with a concentration that produces 50% inhibition of 10 μmol/L (compared with 52 μmol/L for levonorgestrel and 55 μmol/L for dienogest).[19] These findings have gained further support in the clinical setting: in women with acne who were treated with an OC containing norgestimate for 6 months, lesions

improved, skin surface lipid levels decreased, and skin hydration was unchanged.[20] Serum testosterone and progesterone levels decreased over time, and increases in sex hormone-binding globulin levels were observed.

The interaction of progestins with enzymes such as sulfatase, aromatase, and 17β-hydroxysteroid dehydrogenase in breast tissue may have implications for breast cancer etiology, progression, and therapy.[21] Local action of estradiol within the breast tissue could have a (still controversial) role in promoting the growth and evolution of tumors. Therefore, blocking the breast enzymes that are involved in the biosynthesis of estradiol from existing precursors may prevent interaction between estradiol and cancer cells. *In vitro* studies have demonstrated that norelgestromin is able to inhibit estrone sulfatase and 17β-hydroxysteroid dehydrogenase activity in breast cancer cells,[21] thereby suggesting a potential protective effect on the breast tissue.

3. Key Issues in Contraception

3.1 Effectiveness

One of the key issues in choosing an appropriate contraceptive is ensuring that the efficacy demonstrated in clinical trials is able to be translated into effectiveness in the real world. Effectiveness is usually a function of the efficacy of the contraceptive in combination with compliance with its dosing regimen.[1-3]

3.1.1 Efficacy

The efficacy of the transdermal contraceptive patch has been established in three pivotal phase III studies: one multicenter, open-label, non-comparative study[6] and two randomized, multicenter, open-label comparisons with an OC.[7,8] The non-comparative study included 1754 healthy, ovulatory, sexually active women who received the contraceptive patch for six cycles (approximately two-thirds of participants) or 13 cycles (approximately one-third of participants).[6] During each cycle, a new patch was applied to the buttock, upper outer arm, lower abdomen, or upper torso (excluding the breast) every 7 days for 3 weeks, followed by one patch-free week. In the event of accidental patch detachment, women were instructed to immediately apply a replacement patch for the remainder of the week. Six pregnancies occurred in the 1664 women included in the efficacy analysis (10 994 cycles), five of which were attributed to method failure (conception occurred while the woman was perfectly compliant with the contraception method), and one was attributed to user failure (conception occurred when the woman did not comply with the contraceptive regimen). The overall Kaplan-Meier estimates of the cumulative probabilities of pregnancy over cycles 1–6 and cycles 1–13 were 0.4 (95% CI 0, 0.7) and 0.7 (95% CI 0, 1.4), respectively, and the method-failure probability of pregnancy was 0.4 (95% CI 0, 0.7) over both cycles 1–6 and 1–13. Based on the results of this study, the overall Pearl Index (the number of pregnancies per 100 woman-years of use) for the contraceptive patch was 0.71 and the method-failure Pearl Index was 0.59.

The efficacy of the transdermal contraceptive was further supported by two comparative studies with OCs. In the first study, 1417 sexually active women were randomized to treatment for 6 or 13 cycles using the contraceptive patch (administered in the same way as previously described) or a triphasic OC containing ethinylestradiol/levonorgestrel (Triphasil®: 30μg/50μg days 1–6; 40μg/75μg days 7–11; 30μg/125μg days 12–21).[7] In the 811 women in the patch group, over 5240 cycles, four pregnancies occurred due to method failure and one occurred due to user failure, with four pregnancies due to method failure and three due to user failure occurring in 605 women over 4167 cycles in the OC group. These results translated into a lower overall Pearl Index (1.24 vs 2.18, respectively) and a similar method-failure Pearl Index (0.99 vs 1.25, respectively) for the patch compared with the OC; however, the between-treatment differences did not reach statistical significance.[8] In the second comparative study, the contraceptive efficacy of the patch was similar to that offered by an ethinylestradiol/desogestrel OC (Mercilon®; 20μg/150μg).[8] One pregnancy due to user failure and three due to method failure occurred in the 861 women randomized to the patch, with one pregnancy due to user failure and one due to method failure reported in the 656 women receiving the OC. Pearl Indices were similar between the patch and OC regimens, with overall indices of 0.88 and 0.56, respectively, and method failure indices of 0.66 and 0.28, respectively.[7]

In order to more accurately estimate contraceptive efficacy, data from the three pivotal transdermal patch studies were pooled,[22] giving an overall Pearl index of 0.88 (95% CI 0.44, 1.33), with a method failure Pearl index of 0.70 (95% CI 0.31, 1.10) [table I].[22]

3.1.2 Compliance

Imperfect compliance is the primary reason used to explain the difference between the contraceptive effectiveness seen with the OC in clinical trials and that in the real world;[1,2] indeed, it has been estimated that a first-year failure rate of 0.1% is associated with correct use of the OC[24] compared with a 7.3–8.5% failure rate with typical use.[25] Compliance with hormonal contraception is a particular issue for adolescents.[26]

Analysis of data from the two randomized studies comparing the contraceptive patch to an OC showed that compliance was significantly greater with the patch compared with the OC. In the study by Audet et al.,[7] perfect compliance was reported in 88.2%

Table I. Pregnancy rates and Pearl Indices across three pivotal phase III trials of the ethinylestradiol/norgestromin transdermal contraceptive patch[6-8,22] (reproduced from Burkman,[23] Copyright 2004, with permission from Elsevier)

Study	No. of cycles	No. of pregnancies	Overall Pearl Index	Method-failure Pearl Index
Smallwood et al.[6]	10 994	6	0.71	0.59
Audet et al.[7]	5 240	5	1.24	0.99
Hedon et al.[8]	5 921	4	0.88	0.66
Pooled analysis[22]	22 155	15	0.88	0.70

of participant's cycles compared with 77.7% with the OC ($p < 0.001$). Similarly, in the study from Hedon et al.,[8] perfect compliance was higher in patch users (94.4% of cycles) compared with OC users (87.8%). Retrospective analysis of data from women enrolled in North American centers in both studies further confirmed superior compliance with the contraceptive patch (88.7% vs 79.2%, respectively; $p < 0.001$).[27,28] Not surprisingly, contraceptive efficacy was significantly better with perfect administration compared with imperfect administration, regardless of whether participants were using the patch or OC.

When analyzed according to age, perfect administration was consistently high in all age groups with the patch, but was poorer in younger OC users than older participants (figure 1).[28] This finding led to further evaluation of compliance rates and the acceptability of the patch in younger users. In a three-cycle study in 50 sexually active adolescents aged 15–18 years, 87.1% of the 31 individuals who were followed up at 3 months reported perfect compliance with patch use.[29] Most participants reported that they liked using the patch and 24 of 31 participants wished to continue using it as their primary mode of contraception. The most strongly endorsed benefits of the patch were that it was easy to use and easy to hide. Compliance was also considered to be excellent in a clinical review of data from 62 adolescent women followed for a mean of ten cycles.[30]

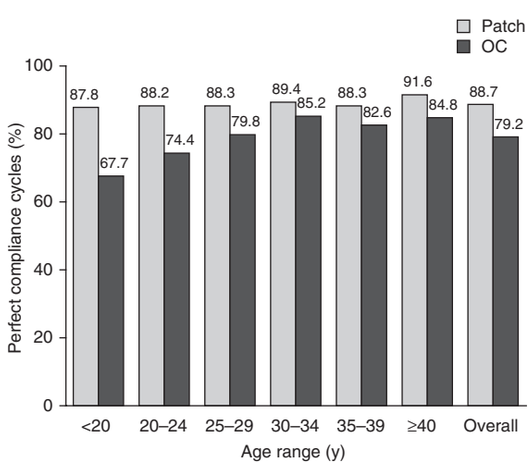

Fig. 1. Contraceptive compliance by age group in women enrolled in the North American centers of the two pivotal comparative studies of the transdermal contraceptive patch vs an oral contraceptive (OC).[28] In the OC group, the difference in compliance across the age groups was statistically significant ($p < 0.001$).

According to the evaluation of preference for, and satisfaction with the contraceptive patch in a nine-cycle observational study conducted in Canada, almost 75% of women preferred the patch to their previous method of contraception, mainly because of its simplicity and convenience.[31] Perfect compliance was high across all cycles (88%) and did not differ significantly across age groups in eight of nine cycles.

3.2 Safety and Tolerability

The safety of hormonal contraception has been questioned in recent years, particularly with respect to an increased risk of venous thromboembolic events associated with third-generation agents.[32] However, post-marketing safety studies of OCs containing ethinylestradiol and norgestimate show that the numbers of adverse events with these agents are very low.[33] In addition, a recent nested case-control study among women aged 15–44 years concluded that the risk of non-fatal venous thromboembolism was similar between the contraceptive patch and norgestimate-containing OCs with 35μg of ethinylestradiol.[34] In recognition of the difficulty associated with communicating risk in practical terms, and the associated perception issues, the Council for International Organizations of Medical Sciences task force of the WHO released a report in 1998, which provides a standardized risk categorization to assist healthcare professionals and the public in the interpretation of risks.[35] In this context, risks are considered as follows: <1/1000 = rare; <1/10 000 = very rare.

The overall risks associated with hormonal contraception are therefore in the category of very rare events, with a more favorable safety profile associated with norgestimate. In fact, North American post-marketing data (published in 1997) showed that while >47 million cycles of norgestimate-containing OCs have been prescribed, only 13 non-fatal cardiovascular events have been reported in women receiving this form of contraception.[33] No further cardiovascular safety signals have been raised in association with norgestimate-containing contraceptive methods since this publication.

Pooled analysis of data from the pivotal phase III studies of the contraceptive patch indicate that it is well tolerated with a similar adverse event profile to the OC.[9] Rates of headache, nausea, and abdominal pain did not show statistically significant differences between treatment groups. Patch users had a higher rate of breast symptoms (breast discomfort, breast engorgement, and breast pain) than OC users; however, this difference was only significant for cycles 1 and 2 ($p < 0.001$). By cycle 13, the incidence of breast symptoms in the patch group had reduced to 0%. Furthermore, breast symptoms were largely rated as mild or moderate in severity, with <1% of women in either group discontinuing treatment for this reason. A higher rate of dysmenorrhea was also reported with the contraceptive patch ($p = 0.04$); however, this was regarded as a treatment-limiting event in <1% of participants.

Application-site reactions were reported in 17.4% of women in the three phase III contraceptive patch studies.[9] Most application-site reactions were mild or moderate in severity (91.6%) and <2% of participants discontinued treatment for this reason.

Across all three studies, seven serious adverse events were reported (0.2% of participants) that were possibly, probably, or likely related to the contraceptive patch: one case each of menorrhagia; pain, hypesthesia, and paresthesia; cholecystitis; cervical carcinoma in situ; and migraine; and two cases of non-fatal pulmonary embolism.[9] In all participants, the events resolved spontaneously, with appropriate treatment or after patch withdrawal.

As with other combined contraceptive methods, use of the ethinylestradiol/norelgestromin patch is contraindicated in women with present or previous venous thrombosis (with or without the involvement of pulmonary embolism); present or previous arterial thrombosis; migraine with a focal aura; serious or multiple risk factors for arterial thrombosis (such as severe hypertension, diabetes mellitus with vascular involvement, or hereditary dyslipoproteinemia); possible hereditary disposition for venous or arterial thrombosis; known or suspected carcinoma of the breast or endometrium or any other estrogen-dependent neoplasia; abnormal liver function related to acute or chronic hepatocellular disease; hepatic adenomas or carcinomas; or genital bleeding without a diagnosed cause.[11]

3.2.1 Cost Effectiveness

The implications of increased perfect use with the contraceptive patch compared with OCs in terms of cost effectiveness was examined in the base case of a recent model analysis using data from the two phase III contraceptive patch versus OC studies.[36] Insurance payments from a large administrative claims database were used as proxies for costs. This analysis represented women aged 15–50 years in long-term, mutually monogamous relationships and showed that the contraceptive patch resulted in savings of $US249 (2002 values) and 0.03 pregnancies per woman over 2 years compared with an OC, based on a Pearl Index of 0.87 for the contraceptive patch and 1.33 for the OC (figure 2). Most of the difference in cost was due to the cost of an unwanted pregnancy. A sensitivity analysis showed that cost savings were greatest for those in the youngest age group. The relationship between cost effectiveness and compliance was further explored by considering the differences in imperfect cycles per year. The rate was held constant for the patch (1.5 cycles/year) and it was shown that the threshold above which the patch was cost saving was 1.22 imperfect OC cycles/year. Given that the lowest observed rates of imperfect cycles with OC was 1.9 cycles/year in the comparative contraceptive studies, this validates the cost effectiveness of the patch in the typical-use setting. Whether the findings of this base-case analysis can be generalized to comparisons with all OCs is unclear, as it was based on two randomized clinical trials that utilized the ethinylestradiol/levonorgestrel and ethinylestradiol/desogestrel OCs. Furthermore, it is likely that more imperfect cycles would be observed outside of the clinical trial setting, which would likely impact the number of pregnancies. Nevertheless, this quantified economic advantage of the contraceptive patch should be added to the emotional costs of an unwanted pregnancy that occurs in spite of the use of a contraceptive method. This combined cost further underlines the importance of methods that improve compliance and reduce the rate of user-related failures.

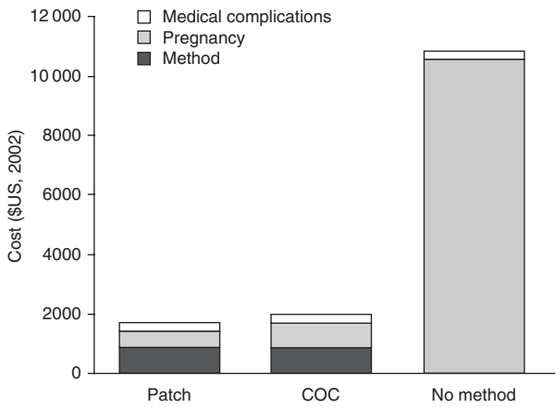

Fig. 2. Cost components of contraceptive method use over 2 years, based on a base-case analysis using data from the two phase III, randomized studies of the contraceptive patch vs the combined oral contraceptive (COC) [reproduced from Sonnenberg et al.,[36] Copyright 2005, with permission from Elsevier].

4. Conclusions

Contraceptive choice should be based on the clinical profile of the contraceptive and suitability for the patient. The norelgestromin-containing contraceptive patch is an effective method of

contraception with efficacy and tolerability that is comparable to that of marketed OCs. The patch offers the added benefits of steady serum concentrations of contraceptive, once-weekly administration, and improved compliance with treatment.

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