

Adherence to a flexible extended regimen for oral hormonal contraception provided in blister packaging compared with an adherence-supporting digital tablet dispenser: historical comparison of data from two clinical studies

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Background: The Clyk™ digital pill dispenser helps ensure correct and consistent administration of a flexible extended regimen of the combined oral contraceptive, ethinylestradiol (EE) 20 µg/drospirenone 3 mg (EE/drospirenone_{Flex}; YAZ® Flex), guiding users through the intake cycle and 4-day pill break and providing visible and acoustic daily reminders when pill intake is due. A study showed that the audible alarm function of the dispenser could help reduce the number of missed pills, but it lacked an appropriate “non-dispenser” group for a meaningful assessment of the impact of the dispenser on adherence. This study indirectly assessed the overall effect of the digital dispenser on adherence by comparing data from a treatment with standard blister packaging.

Materials and methods: One-year adherence data were compared from two similarly designed, Phase III, open-label, randomized trials of EE/drospirenone_{Flex}. In study 1, women used diary cards to record adherence with EE/drospirenone_{Flex} dispensed in blister packs (n=640), and in study 2 the dispenser was used with the alarm activated (n=250) or deactivated (n=248) in addition to using diary cards.

Results: A mean (±SD) of 4.3 (±4.24) missed pills over 1 year were recorded in diary cards among women who dispensed their pills from the blister packages (study 1) compared with 1.0 (±2.4) recorded by the alarm-activated dispenser (study 2). In study 2, a mean of 1.9 (±4.4) missed pills were reported in the diaries over 1 year compared with 4.4 (±9.1) from automatic recording by the dispenser (both arms of study 2), indicating underreporting of missed pills in diary cards vs the digital dispenser. Adjusting for this rate of underreporting, an estimated mean of ten pills were missed over 1 year by women using EE/drospirenone_{Flex} in blister packs, or ten times more than with the digital dispenser with activated acoustic alarm.

Conclusion: The digital dispenser helps reduce the number of missed pills and increases adherence.

Keywords: compliance, contraception, drospirenone, ethinylestradiol, flexible extended regimen, efficacy, pill dispenser

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Introduction

Extended regimens of combined oral contraceptives (COCs) may be the preferred birth control option for women who prefer fewer menstruations, as well as for non-contraceptive medical reasons such as dysmenorrhea, endometriosis, abnormal

uterine bleeding, hemorrhagic diathesis, and menstrual migraine.^{1,2} Flexible extended regimens of COCs are designed to enable extended pill intake and to reduce the number of menstrual periods per year or schedule the menstrual bleeding (withdrawal bleeding) according to the needs of the woman, while managing breakthrough bleeding associated with extended regimens.^{3,4} Clinical studies provide some evidence that extended regimens could be associated with better contraceptive efficacy than standard cyclic oral contraceptive regimens.^{3,5} Fewer hormone-free intervals reduce the risk of escape ovulation because of missed pills in the days before or after the hormonal withdrawal. The CORALIANCE study showed that, among women taking a pill involving a treatment-free interval, the rate of missing a pill was high (42%) in the first week after resuming therapy. In fact, 18% missed taking the first pill and 24% missed a pill during the first week of resuming therapy after a treatment-free interval.⁶ Assuming that contraceptive failure is mostly associated with low intake adherence (ie, missed pills), the adherence pattern and possible differences resulting from packaging with different levels of adherence support are worth investigating.

A flexible extended regimen of the oral hormonal contraceptive, ethinylestradiol (EE) 20 µg/drospirenone 3 mg (EE/drospirenone_{Flex}; YAZ® Flex), with cycle lengths that may vary between 28 days and 124 days, including a 4-day pill break, has been approved in the European Union and other countries. Comparative studies have demonstrated that EE/drospirenone_{Flex} is well tolerated and has good contraceptive efficacy and significantly fewer bleeding days than conventional 28-day or fixed long-cycle 124-day COC regimens.⁷⁻¹⁰

Poor compliance is a common issue among COC users,^{6,11,12} and it is associated with unintended pregnancy;¹³ a large European study demonstrated that women who missed one or more pills a month were 2.6 times more likely to have an unintended pregnancy than those who did not miss any pills.¹⁴ The digital dispenser, Clyk™, was developed for use with EE/drospirenone_{Flex} to help ensure correct and consistent pill administration within a flexible regimen. It guides users through the intake cycle and the 4-day pill break, providing visible and acoustic daily reminders when pill intake is due. In addition, the dispenser provides guidance on what to do if pills are missed. If too many pills have been missed, the dispenser shows a warning that contraceptive protection may be jeopardized and provides instructions on what to do to regain full contraceptive protection. It should be noted that the dispenser is battery powered with a 2-year shelf life and does not require recharging; therefore, potential loss of functionality is not a concern. The effect of the digital dispenser with the acoustic alarm function either activated or deactivated

on adherence with EE/drospirenone_{Flex} was assessed in a 12-month open-label, randomized, European study (France, Germany, Italy, Spain, and the UK) involving 499 women.¹⁰ The acoustic alarm of the digital dispenser substantially reduced the number of missed pills.^{10,15} The study did not include a “non-dispenser” comparator group to allow for an assessment of the overall effect of the dispenser on adherence. However, in addition to the automatic recording of adherence data by the digital dispenser, the study used a standard method of a paper diary to collect patient-reported adherence data in order to allow historic comparisons. A previous clinical study of EE/drospirenone_{Flex} using standard blister packaging included a treatment group that followed the same flexible extended regimen as described earlier,¹⁰ but in this study the women used paper diary cards to track pill intake.⁸ As such, these two studies provide an opportunity to assess indirectly the overall effect of the digital dispenser on adherence.

The objective of this study was to assess the impact of the digital dispenser on adherence by comparing missed pill data from the dispenser alarm-activated and alarm-deactivated groups from the digital dispenser study with historical controls who received EE/drospirenone_{Flex} in blister packs and tracked intake using diary cards in an earlier study. If missed pills are the main reason for contraceptive failure, any reduction in the number of missed pills may help to improve contraceptive efficacy and avoid unintended pregnancies.

Materials and methods

Study design

Design and methodological details of both studies have been published previously,^{8,10} but are outlined briefly in this article. The studies were Phase III, open-label, randomized, parallel-group multicenter trials. Study 1⁸ was conducted between December 2005 and October 2008 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00266032) identifier: NCT00266032), and study 2¹⁰ was conducted between December 2010 and September 2012 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01257984) identifier: NCT01257984). Study 1 consisted of two phases: a 1-year randomized comparative phase⁸ and a 1-year safety extension phase.⁷ Only data from patients in the EE/drospirenone_{Flex} treatment group during the 1-year comparative phase are reported here.

Study population

Both studies enrolled women in general good health, aged 18–35 years (or up to 30 years if smokers) who requested contraception. A normal cervical smear test result at screening or within 6 months prior was also required. Women who were pregnant or lactating, continued use of other contraceptive methods, or had been sterilized were excluded, as were those

with a body mass index ≥ 30 kg/m², a known hypersensitivity to the study drug ingredients, or any disease or condition that could interfere with the study medication or with the conduct of the trial. All women provided written informed consent, and the studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

Treatment

All participants received EE/drospirenone_{Flex} continuously for ≥ 24 days (mandatory phase), followed by pill intake for up to a maximum of 120 consecutive days, then a 4-day pill-free break (Figure 1). Between days 25 and 120 (flexible phase), women could decide to take a 4-day pill-free interval at any time if desired or were advised to take a 4-day pill-free interval if they experienced three consecutive days of intracyclic bleeding. The cycles were repeated for up to 1 year, with each cycle commencing with a mandatory 24-day intake phase after each 4-day pill break, regardless of any ongoing bleeding.

In study 1, medication was provided in blister packs with tablet intake documented using daily diary cards. Participants of study 2 used the Clyk™ digital dispenser to keep track of tablet intake, with the acoustic alarm either activated or deactivated (ie, with reminders given by visual symbol only). At the same time, the digital dispenser tracked the pill release so that the adherence to daily pill intake was documented automatically without any additional action by the woman. A missed pill was identified if there was an interval of 48 hours or more between two pill intakes. In addition, the subjects were asked to document the pill intake in a paper diary. This method of documentation was used to allow a comparison of the adherence data with data from a previous study (study 1), where subjects were using the flexible extended regimen in a standard blister packaging.

The women were provided with instructions for use of the digital dispenser, and women in the activated alarm group were allowed to turn off the acoustic alarm if desired.

Follow-up and outcomes

Follow-up visits were conducted within 4 weeks of study medication initiation, at 3-monthly intervals thereafter, and 18–25 days after study completion or at discontinuation. Routine pregnancy tests were performed at all study visits, and the use of backup contraceptive measures was recorded. Primary and secondary outcomes for both studies were detailed in the original publications and have been fully reported.^{7,8,10}

Statistical analysis

The analysis for this secondary comparative study was descriptive with no hypothesis testing performed. Descriptive statistics (number, mean, and standard deviation [SD]) were calculated for each quantitative variable. A correction for underreporting of missed pills was made using the observed difference between patient-reported data and dispenser-recorded data in study 2.

Results

Baseline characteristics of the participants were similar between the two studies (Table 1). Table 2 summarizes the mean (\pm SD) number of missed pills over 1 year by the study and treatment groups. A mean of 4.3 (± 4.24) missed pills was recorded in diary cards among women in study 1 who dispensed their pills from the blister packages compared with 1.0 (± 2.4) recorded by the dispenser in the alarm-activated group of study 2. Among all participants in study 2, the mean (\pm SD) number of missed pills over 1 year recorded in diary cards was 1.9 (± 4.2) compared with 4.4 (± 9.1) recorded by the digital dispenser. Among women in study 2 who used

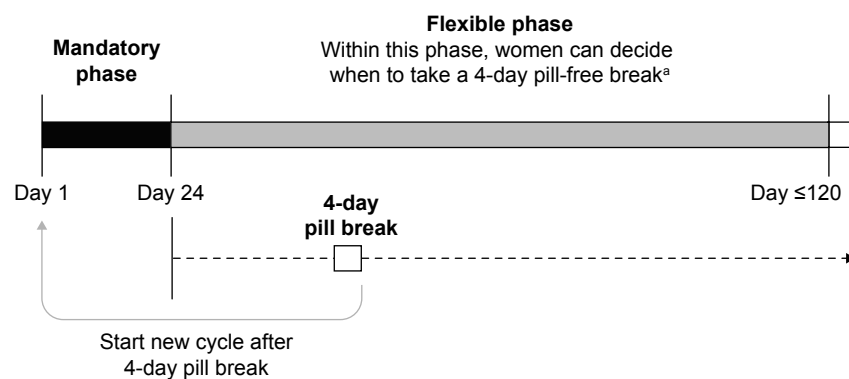


Figure 1 Flexible extended regimen of EE 20 µg/drospirenone 3 mg (YAZ® Flex).

Notes: The regimen requires a minimum of 24 days of continuous pill intake (mandatory phase), after which women decide when to take the 4-day pill-free break any time between days 25 and 120 (flexible phase). ^aWomen were advised to take a 4-day pill-free break if three consecutive days of bleeding or spotting occurred.

Abbreviation: EE, ethinylestradiol.

Table 1 Baseline demographics and clinical characteristics

Characteristics	Study 1: blister packaging (adherence data from paper diary) ⁸	Study 2: dispenser device (adherence data from device and paper diary) ¹⁰	
	Diary card (n=642)	Activated acoustic alarm (n=250)	Deactivated acoustic alarm (n=249)
Mean (SD): age, years	24.8 (4.4)	25.3 (4.3)	25.7 (4.0)
Mean (SD): height, cm	167.2 (6.3)	N/A	N/A
Mean (SD): BMI, kg/m ²	22.5 (2.7)	22.7 (2.9)	22.4 (3.10)
Caucasian ethnicity, n (%)	636 (99.1)	215 (86.0)	216 (86.7)
Smoking status, n (%)			
Never	N/A	146 (58.4)	144 (57.8)
Former	N/A	30 (12.0)	30 (12.0)
Current	205 (31.9)	74 (29.6)	75 (30.1)
Educational level, n (%)			
Elementary	34 (5.2)	5 (2.0)	5 (2.0)
Secondary	289 (45.0)	109 (43.6)	95 (38.2)
College/university	319 (49.7)	136 (54.4)	149 (59.8)
Alcohol consumption, n (%)			
Abstinent	N/A	74 (29.6)	76 (30.5)
Light	N/A	173 (69.2)	165 (66.3)
Moderate	N/A	3 (1.2)	8 (3.2)
Number of pregnancies, n (%)			
0	N/A	193 (77.2)	184 (73.9)
≥1	N/A	57 (22.8)	65 (26.1)
Number of births, n (%)			
0	513 (79.9)	205 (82.0)	198 (79.5)
≥1	129 (20.1)	45 (18.0)	51 (20.5)
Previous contraception, n (%)			
COCs	538 (83.8)	205 (82.0)	213 (85.5)
Condoms	77 (12.0)	28 (11.2)	19 (7.6)
None	17 (2.6)	12 (4.8)	12 (4.8)
Other ^a	10 (1.6)	5 (2.0)	5 (2.0)

Notes: Data indicate the values obtained from all women who received at least one dose of study medication and had at least one clinical observation after the administration of study medication. ^aOther includes vaginal, transdermal, and implant. Adapted by permission from BMJ Publishing Group Ltd. Contraceptive efficacy and tolerability of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen: an open-label, multicentre, randomised, controlled study, Klipping C, Duijkers I, Fortier MP, Marr J, Trummer D, Elliesen J, Volume 38(2), Pages 73–83, Copyright 2012.

Abbreviations: BMI, body mass index; COC, combined oral contraceptives; N/A, not available; SD, standard deviation.

the digital dispenser with the alarm deactivated, the mean number of missed pills recorded in diary cards was 2.8 (±5.3) compared with 7.8 (±11.7) recorded by the digital dispenser. It can therefore be concluded that the amount of underreporting is ~60%, ie, only ~40% of missed pills are reported by the patient in a diary-based compliance documentation (1.9/4.4=0.43). In the study arm with deactivated acoustic alarm, which showed higher frequencies of missed pills, only 36% of missed pills were reported (2.8/7.8=0.36).

Overall, adjusting for underreporting, an estimated actual mean of ten pills (ie, 4.3/0.43=10.0) were missed over 1 year by women using EE/drospirenone_{Flex} dispensed in blister packs (study 1). The actual mean number of missed pills estimated was based on the reported mean number of 4.3 missed pills recorded in diary cards in study 1 multiplied by the underreporting factor observed between the number of missed pills recorded by the women in diary cards (1.9) relative to that recorded by the dispenser (4.4).

Table 2 Mean (SD) number of missed tablets in 1 year by treatment arm

Data source	Study 1 ⁸	Study 2 ¹⁰		All patients (n=498)
	Diary card (n=640)	Activated acoustic alarm (n=250)	Deactivated acoustic alarm (n=248)	
Based on dispenser data	N/A	1.0 (2.5) ^a	7.8 (11.7) ^b	4.4 (9.1) ^c
Based on diary data	4.3 (4.24)	1.0 (2.4)	2.8 (5.3)	1.9 (4.2)

Notes: Data indicate the values obtained from all women who received at least one dose of study medication and had at least one clinical observation after the administration of study medication. The number of missed pills was normalized to 364 days. ^aDispenser data available for 242 participants. ^bDispenser data available for 246 participants. ^cDispenser data available for 488 participants.

Abbreviations: N/A, not applicable; SD, standard deviation.

Discussion

The main reason for contraceptive failure is irregular pill intake with frequent missed pills.¹⁶ Total compliance is difficult to achieve, with up to 81% of women reporting missing at least one pill per cycle, and up to 51% missing three or more pills per cycle.¹⁷ Moreover, missed pills are a source of concern; in a cross-sectional study of 17,091 pill users, 71% of pill users reported noncompliant behavior and 43.9% of the women admitted to being worried because of delayed or missed pills.¹¹ In particular, women are unsure of what to do if they miss more than two pills;^{18,19} thus, a device that advises when extra protection is needed should prove valuable to pill users.

It is reasonable to assume that missed pills may be associated with increased risk of unintended pregnancy. Among the 640 historic controls from study 1, there were a total of four pregnancies during the first year of treatment (Bayer Pharma AG, data on file). Assuming that all of these pregnancies resulted from missed pills, the number of pregnancies can be expressed in relation to the number of missed pills. With 2,752 reported and 6,373 estimated (ie, $2,752 \times 4.4/1.9$) missed pills per year, the average pregnancy rate was one pregnancy per 1,593 missed pills using the estimated true rate of missed pills (ie, $6,373/4$). With the use of the dispenser with the acoustic alarm activated, 3.3 missed pills per woman-year could be prevented on average, or one pregnancy in every 483 women-year of exposure.

Among the 242 women with adherence data from study 2 who received EE/drospirenone_{Flex} using the digital dispenser with an activated alarm with a mean of one missed pill per year of treatment (ie, a total of 242 missed pills), no contraceptive failure was reported. In addition, no failure was reported from the 246 women with adherence data from the other treatment arm using the digital dispenser with deactivated acoustic alarm with a mean of 7.8 missed pills per year (ie, a total of 1,919 missed pills). The missed-pill guidance and the warning function of the dispenser in case of significant adherence failure may have helped women with frequent missed pills to avoid an unintended pregnancy.

A recently updated Cochrane review demonstrated that compliance was similar between extended or continuous cycles of COC and various 28-day regimens, although the authors noted that measurement of compliance through participant diaries has questionable validity.⁵ Several studies have investigated the effects of various reminder methods on compliance in patients receiving COCs. The effectiveness of an email reminder system in improving compliance among 50 new oral contraceptive pill users has been studied.²⁰

Subjects sent a reply email to confirm receipt of the reminder, and compliance was recorded in a diary. A median of 18% (range, 0%–65%) of email reminders were missed, and diary data showed that 20% of 40 evaluable participants missed at least one pill in each cycle.

The use of a reminder card, a credit-card-sized device that emits an audible beep daily for 21 days of a 28-day cycle at a time selected and programmed by the user, was associated with a significant improvement in adherence to oral contraceptives.²¹ A total of 41% of 161 reminder card users reported no missed pills during the 3-month study period compared with 19% of 264 controls. In addition, similarly to our study, comparison of an electronic monitoring device (which recorded each opening of the device) with self-reported compliance revealed underreporting of missed pills.¹⁷ Among 103 women taking oral contraceptives for the first time or resuming after at least 6 months discontinuation, diary data reported an average of 1.0–1.1 missed pills per cycle whereas electronic data reported an average of 2.6 missed pills per cycle. The number of missed pills recorded electronically increased with each cycle from 2.2–2.3 in cycles 1 and 2 to 3.5 in cycle 3.¹⁷

This trend of increasing missed pills with each cycle was also noted in a single-blind, randomized study that examined the effect of daily text message reminders on adherence to oral contraceptives as measured by electronic monitoring device.²² Over three cycles, the number of missed pills was similar between women receiving text reminders and those who did not (4.9 vs 4.6), and comparison of electronic adherence data with daily diaries showed underreporting of missed pills among the entire cohort (4.7 vs 1.2 missed pills per cycle), as well as in both the text-message (4.9 vs 1.9) and control groups (4.6 vs 1.1).²²

Since both studies were conducted in a similar patient population (healthy, fertile women in Europe who are in need of contraception) with a similar methodology for adherence monitoring (paper diaries), we felt that the benefits of this historical comparison outweigh the theoretical limitations. However, it would be ideal if these results could be confirmed in a prospective study.

The use of a correction for underreporting of missed pills may also be seen as a limitation of the study, but we believe that this approach allows for a more accurate comparison of data across studies. Data retrieved from dispenser devices is more reliable than data retrieved from paper diaries (as the potential for human error is reduced), and the number of missed pills recorded by dispenser devices tends to be higher than that recorded using paper diaries. The use of a correction

factor offsets this underreporting and allows the two data sets to be directly compared, giving a more realistic perspective on the issue of nonadherence.

Conclusion

This study investigates the impact of different COC presentations (digital dispenser vs standard blister pack) on adherence and compares the methods used to monitor adherence for each presentation. These results show that, compared with standard blister packs, a digital dispenser (Clyk™) reduces the number of missed pills, which may help reduce contraceptive failure rate in practice.

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Disclosure

Jörg Elliesen and Dietmar Trummer are employees of Bayer Pharma AG. The authors report no other conflicts of interest in this work.

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