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THE ROLE OF DIGOXIN IN TREATING SYSTOLIC HEART FAILURE: AN UPDATE

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Digoxin may be the oldest drug in cardiovascular medicine.¹ In 1875, Sir William Withering published his famous paper on the use of foxglove.² Withering reported the use of a preparation of foxglove leaves to treat “dropsy”.³ Digoxin is the active ingredient in the extract of foxglove leaves. Digoxin has played an important role in treating heart failure and arrhythmias for over 100 years since Withering’s findings. Digoxin is a member of a group of drugs known as cardiac glycosides which have in common some specific effects on the myocardium. Digoxin has been used in the treatment of certain cardiac disorders for many years and labeled for use in chronic heart failure (CHF), atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia. Digoxin is available for oral and intravenous administration. The first commercially available digoxin product was approved by the FDA in 1952. Digitek®, Lanoxin®, Lanoxincaps® and Lanoxin® pediatric are the brand names of digoxin.⁴ Digoxin was approved for treating heart failure in 1998 by FDA on the basis of the PROVED, RADIANCE and DIG clinical trials.¹ The neurohormonal hypothesis in the pathophysiology of heart failure increases use of medications which block the excessive neurohormonal activation such as ACEI, beta-blockers, ARBs and aldosterone antagonists.⁵⁻⁷ Improved survival in patients with heart failure using angiotensin-converting enzyme inhibi-

tors (ACEI)⁸⁻¹², angiotensin receptor blockers (ARB)^{13,14}, beta blockers¹⁵⁻¹⁸ and aldosterone antagonists¹⁹ has been published. The controversy of digoxin use in patients with heart failure was ignited when the DIG trial showed no mortality improvement even though there was a decrease in hospitalization rates.²⁰ Although digoxin use is declining, there has not been a similar decrease in cases of digoxin toxicity.²¹ This paper intends to discuss the pharmacologic effects, pharmacokinetic characteristics, and toxicity of digoxin and some key clinical trials regarding its use in heart failure patients.

Effects of Digoxin

The pharmacologic actions of digoxin remained obscure for a long time. Digoxin was first considered to have diuretic properties. In 1938, Cattle and Gold found that digoxin has direct inotropic effects and this became the accepted mechanism of action.²² However, recognition of digoxin’s effect has changed drastically with the enhanced understanding of the pathophysiology of heart failure.²² Digoxin has multiple pharmacologic effects in addition to its positive inotropic function.

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Positive Inotropic Effect

Digoxin reversibly binds to and inhibits the alpha subunit of sodium-potassium ATPase which pumps sodium out and potassium into cells. Thus, transmembrane sodium gradient is reduced. Since a low intracellular sodium concentration drives the action of the sodium-calcium exchanger, by inhibiting sodium-potassium ATPase, digoxin indirectly inhibits the action of the sodium-calcium exchanger. This leads to higher intracellular calcium, which increases myocardium contractility.²² Based upon this mechanism, digoxin should benefit patients with systolic heart failure characterized by impaired ventricular contractility.

Neurohormonal Effect

Previous studies demonstrated that digoxin significantly decreased serum norepinephrine, renin and aldosterone concentration in heart failure patients.^{23, 24} These effects are beneficial to heart failure patients in whom neurohormonal activation is frequently present.

Autonomic Effect

Chronic heart failure is characterized by increased sympathetic activity and decreased parasympathetic activity.²⁵ Long term use of digoxin sensitizes cardiac and aortic baroreceptors.^{26, 27} Along with decreased norepinephrine, sensitized baroreceptors lead to decreased sympathetic tone.²⁸⁻³⁰ In addition, digoxin increases parasympathetic tone.³¹

Diuretic Effect

Digoxin inhibits sodium-potassium ATPase in the kidney which leads to inhibition of sodium reabsorption. Digoxin indirectly improves renal perfusion by increasing cardiac contractility.^{32, 33}

Electrophysiological Effect

Digoxin has vagomimetic action on the sinoatrial (SA) and atrioventricular (AV) nodes. It slows heart rate and decreases conduction velocity through the AV node.³⁴

Pharmacokinetics of digoxin

Oral digoxin is absorbed by passive diffusion in the upper small intestine.³⁵ Food may delay the absorption of digoxin, but does not affect the extent of absorption. The bioavailability of digoxin varies slightly in terms of formulation. The bioavailability of

the elixir is 75-85%, the tablet is 70-80%, while the capsule is 90-100%.³⁵ The distribution phase is 6-8 hours long. Approximately 30% of digoxin is protein bound. Digoxin is concentrated in tissue and therefore has large volume of distribution. The volume of distribution (Vd) of digoxin is 6-7L/Kg in patients with normal renal function.³⁵ But age, renal impairment, concomitant drug use and some disease states could affect the Vd of digoxin, which in turn alters the effects and toxicity of digoxin (**Table 1**). Only 16% of a digoxin dose is metabolized. The end metabolites, which include 3 β -digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. Digoxin is not known to induce or inhibit the cytochrome P-450 system.³⁶ In about 10% of population, gut bacteria may convert up to 40% of oral digoxin dose to inactive product. As a result, some antibiotics may affect the serum concentration of digoxin by inactivating the gut bacteria. Fifty to seventy percent of a digoxin dose is excreted unchanged in the urine. The elimination half-life is dependent on age, renal and cardiac function. Cardiac disease, advanced age and kidney disease are associated with diminished creatinine clearance and with decreased renal clearance of digoxin. Digoxin has a half-life of 38-48 hours in patients with normal renal function and extends to 4-6 days when patients have compromised renal function.³⁵

Digoxin interacts with many medications through different mechanisms. Some medications, such as magnesium and potassium-depleting diuretics, can precipitate digoxin toxicity by decreasing serum potassium. Beta-adrenergic blockers or non-dihydropyridine calcium channel blockers may have an additive effect on heart rate when used in combi-

Table 1. Volume of distribution of digoxin in different patient groups

Patient groups	Vd (L/Kg)
Adults with normal renal function	6-7
Neonates	7.5-10
Children	16
Adults with chronic renal failure	4-6
Hyperthyroidism	↑ Vd
Hyperkalemia and Hyponatremia	↓ distribution to the heart and muscle
Hypokalemia	↑ distribution to the heart and muscle
Concomitant quinidine therapy	↓ Vd

nation with digoxin. Some antibiotics such as macrolides and tetracyclines increase digoxin serum levels by inhibiting conversion to inactive product by gut bacteria. Many medications affect digoxin serum level by disturbing its absorption. Rifampin can decrease digoxin serum levels by increasing its non-renal clearance. Amiodarone increases digoxin serum levels. When starting amiodarone in patients taking digoxin, an immediate reduction of digoxin dose by 50% is warranted. Quinidine displaces digoxin from tissue binding sites and inhibits its renal clearance, which leads to increased digoxin concentration.³⁷ There are also many medications which affect digoxin concentration with undefined mechanisms (Table 2).^{35,36}

When dosing digoxin, there are several factors to be considered. Dose should be calculated based upon lean body weight. Age, renal function, diseases and concomitant drug use are all likely to change the pharmacokinetic and pharmacodynamic profiles of digoxin (Table 3).³⁸ Establishing the optimal dose of digoxin is very important since digoxin has a narrow therapeutic range. The digoxin concentration of 0.125 mg - 0.25 mg/day is often used to achieve a serum concentration of 0.5-1.0 ng/ml in patients with heart failure.¹ Serum concentration should be monitored due to its high risk of toxicity. Since the half-life of digoxin is about 2 days in patients with normal renal function, the steady state concentration is obtained after approximately 10 days of initiation. Any serum concentration obtained sooner than 8 hours after the last dose is uninterpretable because this time period reflects the distri-

bution phase of digoxin, which is not appropriate for clinical decision making.¹ If steady state concentration is therapeutic, frequent serum concentration monitoring is unnecessary unless signs and symptoms of toxicity are suspected, the patient's renal function changes, or an interacting drug is added or removed.

Adverse Reactions of Digoxin

Among all digoxin adverse reactions, cardiac adverse events account for 50%, gastrointestinal disturbances for about 25%, and CNS and other toxicity for the remaining 25%.³⁶ Cardiac events include tachycardia, bradycardia, AV block and ventricular fibrillation. Gastrointestinal manifestations include nausea, vomiting, diarrhea and anorexia. CNS reactions include visual disturbances, hallucination, headache, dizziness and confusion. Gynecomastia, thrombocytopenia and skin reactions have also been observed, but incidences are rare.³⁶

Treatment of Digoxin intoxication

When toxicity of digoxin is suspected, a valid serum concentration should be measured to confirm toxicity. If the elevated concentration is thought to cause toxicity, digoxin should be discontinued. If hypokalemia or hypomagnesemia are identified, the electrolyte disturbances should be corrected. Patients with symptomatic bradyarrhythmias should be treated with atropine.¹ Patients with life-threatening ventricular arrhythmias or heart block should be administered Digibind[®] to reverse toxicity. Digibind[®] is purified antidigoxin Fab fragments from digoxin-

Table 2. Medication interactions with digoxin

Increased effects or toxicity of digoxin		Decreased effects of digoxin	
Mechanism	Medications	Mechanism	Medications
Precipitate hypokalemia	HCTZ, loop diuretics	Interfere with small intestine absorption	Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine, certain anticancer drugs, metoclopramide, and food
Additive effects on HR, AV blockade	Beta-adrenergic blockers, DHP-calcium channel blockers		
Decreased conversion to inactive products by gut bacteria	Macrolides, tetracyclines	Increase non-renal clearance	Rifampin
Decrease GI motility	Propantheline, diphenoxylate	Increase metabolism rate	Synthroid [®] in patients with hypothyroidism
Increase risk of arrhythmia	Succinylcholine		
Reduce renal clearance or volume of distribution	Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone		

HR-Heart Rate; AV-Atrium Ventricle; GI-Gastrointestinal; HCTZ-Hydrochlorothiazide; DHP-Dihydropyridine.

Table 3. Situations in which digoxin dose requires adjustment.

Situation	Dose adjustment
Concomitant use with amiodarone	Reduce digoxin dose by 50%
Concomitant use with quinidine	Reduce digoxin dose by 33-50%
Clcr 10-50mL/min	Administer 25-75% of dose or dose every 36 hours
Clcr <10mL/min	Administer 10-25% of dose or dose every 48 hours
ESRD	Reduce digoxin dose by 50%
Concomitant use with Synthroid®	Increase digoxin dose when initiating Synthroid®
Switching from oral digoxin (tablets, elixir) to IV digoxin	Reduce IV digoxin dose by 20-25%

Clcr - creatinine clearance; ESRD - end stage renal disease; IV - intravenous.

specific antisera. Reinitiation of digoxin may be considered when the symptoms of toxicity resolve and the underlying factors are addressed.^{1,39}

Major Clinical Trials

In spite of its long history in cardiovascular medicine, the FDA approval of digoxin for treating heart failure was relatively recent. The approval was on the basis of several clinical trials: the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED), Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme (RADIANCE), and Digitalis Investigators Group (DIG). The trials provide compelling evidence in favor of digoxin use in the treatment of symptomatic chronic heart failure.^{20, 40-41}

Prior to these three trials, several controlled studies conducted in the 1980's demonstrated that digoxin improved the symptoms and exercise tolerance of patients with normal sinus rhythm whose ventricular systolic function is impaired.⁴²⁻⁴⁴ Using a randomized, double-blind, crossover protocol, Lee et al. found that long-term digoxin therapy is clinically beneficial in patients with heart failure, unaccompanied by atrial fibrillation, whose symptoms persist despite diuretic therapy.⁴⁴ In another randomized, double-blind, crossover trial, the digoxin treatment group showed greater improvement in patients with CHF and normal sinus rhythm regarding dyspnea, walking test score, ejection fraction and clinical assessment of CHF compared to placebo group.⁴² A multicenter, double-blind, placebo-controlled study was conducted by the Captopril-Digoxin Multicenter Research Group in 1988. Patients with mild to moderate heart failure received maintenance diuretic therapy. Captopril significantly improved exercise time (mean increase, 82 s vs 35 s) and New York

Heart Association class (41% vs 22%) compared to placebo, while digoxin therapy did not. However, digoxin treatment achieved greater left ventricular ejection fraction increase (4.4%) than captopril (1.8% increase) or placebo (0.9% increase).⁴³

PROVED was a prospective, placebo-controlled, double-blind digoxin withdrawal trial. The aim was to determine whether digoxin is effective in patients with chronic, stable, mild to moderate heart failure. Patients were in normal sinus rhythm and received long-term treatment with diuretics and digoxin. Digoxin withdrawal resulted in worsening of maximal exercise capacity, an increased incidence of treatment failure, and decreased time to treatment failure compared with continuation of digoxin.⁴⁰

In RADIANCE, patients were receiving not only diuretic and digoxin, but also and ACE inhibitor (ACEi)(captopril or enalapril). Similar to PROVED, patients in RADIANCE had New York Heart Association class II or III heart failure and left ventricular ejection fractions of 35% or less in normal sinus rhythm. Digoxin discontinuation was associated with lower quality of life scores, decreased ejection fraction, and increases in heart rate and body weight. The digoxin withdrawal group had a 5.9-fold higher risk of worsening heart failure. In addition, maximal exercise tolerance and submaximal exercise endurance were reduced in patients discontinuing digoxin.⁴¹

A meta analysis of PROVED and RADIANCE was conducted. Data suggested that worsening heart failure occurred more often in patients on an ACEi plus diuretic therapy, digoxin plus diuretic therapy, or diuretic alone compared to triple therapy (ACEi, diuretic, and digoxin).⁴⁵

The DIG trial was a large, international, placebo-controlled trial that included two sub-studies, DIG-Main and DIG-Ancillary.²⁰ A total of 7,788 pa-

Table 4. Baseline characteristics and clinical outcomes of PROVED⁴⁰, RADIANCE⁴¹ and DIG trials.²⁰

Patients baseline or clinical outcomes with digoxin	PROVED TRIAL	RADIANCE TRIAL	DIG TRIAL
Concomitant therapy	Diuretics	ACEI and diuretics	ACEI (95%) or Diuretics (82%)
Treatment	Digoxin withdrawal	Digoxin withdrawal	Add digoxin
Patients	NYHA class II-III and LVEF <35%	NYHA class II-III and LVEF <35%	NYHA class I-IV
Duration of study (weeks)	12	12	148
Average Serum Digoxin Level (ng/ml)	1.2	1.2	0.9
Incidence of worsening HF	Decreased	Decreased	Decreased
Incidence of hospitalization for HF	Decreased	Decreased	Decreased
Exercise time	Increased	Increased	NA
LVEF	Higher	Higher	NA
Time to treatment failure	Increased	Increased	NA
Body Weight	Decreased	Decreased	NA
Heart Rate	Decreased	Decreased	NA
All cause Mortality	NA	NA	No effect
Mortality due to Heart failure	NA	NA	Slightly decreased

LVEF - left ventricular ejection fraction

New York Heart Association (NYHA) Classification:

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings discomfort and symptoms occur at rest.

tients were enrolled in the trial, including 6,800 patients in the main trial, and 988 in the ancillary trial. The DIG-Main study determined the effect of digoxin on all-cause mortality in patients with clinical heart failure who were in sinus rhythm and whose ejection fraction was less than 45%. The DIG-Ancillary study examined the effect in those with an ejection fraction greater than 45%. Secondary outcomes evaluated in this large trial included hospitalization for worsening heart failure, cardiovascular mortality, deaths due to progressive heart failure and hospitalizations for all other causes, including digoxin toxicity.²⁰

In the DIG trial, digoxin had no effect on overall mortality or cardiovascular mortality. Digoxin treatment was associated with a modest reduction in all-cause hospitalizations (6%), substantial reductions in HF hospitalizations (27%) and in HF mortality or hospitalizations (24%).²⁰ Digoxin was more beneficial in patients with lower ejection fractions (< 25%), enlarged hearts, and NYHA functional classifications III or IV.²⁰ With respect to toxicity, more patients in the digoxin group had sus-

pected digoxin toxicity (11.9% vs 7.9%) and were hospitalized due to the toxicity (16.5% vs 11.4%) compared to the placebo group. The most common manifestations of digoxin toxicity included ventricular fibrillation, tachycardia, supraventricular arrhythmia, and second- or third degree atrioventricular block.²⁰

In a comprehensive pos-hoc analysis of the DIG trial, the effect of digoxin on outcomes was studied as a function of the serum digoxin concentration (SDC). Lower SDCs (0.5-0.9 ng/ml) were associated with reduced all-cause mortality (29.3% vs 32.9%), cardiovascular mortality (24.1% vs 25.5%) and HF hospitalization compared to placebo (8.8% vs 12.1%), whereas high SDCs (> 1.0 ng/ml) were associated with increased risk in all three outcomes (41.7%, 33.2% and 13.6%). Low SDCs did not reduce all-cause mortality in some subgroups of patients, including women or non-white patients, patients not receiving ACE inhibitors, patients with NYHA I or II functional class, or ejection fraction > 45%. In this study, predictors of high SDC were identified as advanced age, female gender, renal dys-

function, use of non-potassium sparing diuretics, and pulmonary congestion. This study suggested that low concentration digoxin would be most beneficial in men with moderate to severe systolic heart failure receiving ACE inhibitors.³⁸ Table 4 summarizes the main characteristics and outcomes in the three major trials.

Controversy in Digoxin Trial Cohorts

Women with heart failure tend to be more symptomatic than men with similar ejection fractions.⁴⁶ The majority of deaths attributable to heart failure occur in women.⁴⁷ Although women made up 22% of the study population¹, digoxin did not provide benefit in women with heart failure. One post-hoc study suggested that digoxin was associated with an increased risk of death, death from cardiovascular causes or death from worsening heart failure in women. Digoxin had a small impact on reduced hospitalizations for worsening heart failure in women.⁴⁸ In another post-hoc analysis of DIG trial, female gender was a risk factor for high serum digoxin concentrations and even low SDCs did not decrease mortality.³⁸

With age, the incidence and prevalence of heart failure increase substantially. In the DIG trial, although advanced age is a predictor of higher SDC³⁸, it is not associated with an increased occurrence of digoxin toxicity.⁴⁸ The findings of reduced all-cause hospitalizations, reduced HF hospitalizations and a neutral effect on mortality are consistent in all age groups.⁴⁸ Digoxin remains a useful treatment in elderly patients with heart failure. Due to reduced lean body mass and declining renal function, a lower dosage of digoxin would be appropriate.

Summary

Although digoxin had no effect on mortality in patients with heart failure, it reduced hospitalizations. Digoxin remains a useful agent in treating heart failure. Digoxin could be used as adjunct therapy in patients who still have symptoms while taking an ACEI or ARB and/or a beta-blocker. Digoxin can reduce hospitalizations and decrease the risk of death when dosed at a lower concentration (0.5-0.9 ng/ml). Digoxin may be more beneficial in patients whom have lower ejection fractions (< 25%), enlarged hearts, and are NYHA functional class III or IV. Women with heart failure seem to have reduced benefit from digoxin compared to men.

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TRADITIONAL VS. LOW-DOSE ORAL CONTRACEPTIVES

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More than 10 million American women use oral contraceptives annually. With over 40 brands on the market, patients and practitioners have options when selecting “The Pill” that is right for them. When choosing an oral contraceptive agent, the goal is to select a pill that will provide the lowest effective dose with the least amount of side effects. While the progestin component of combined oral contraceptives (COC) varies greatly, the estrogen component, ethinyl estradiol (EE), is available in essentially two categories: traditional (≥ 30 mcg/24 hr EE) or low-dose (< 30 mcg/24 hr EE). Currently marketed low-dose regimens are displayed in Table 1. The introduction of low-dose estrogen pills has raised the question of whether they offer any significant advantage over traditional pills.

The accepted dose of estrogen has changed over time. Enovid 10[®], the first birth control pill, contained 105 mcg of ethinyl estradiol (EE) equivalent when it was introduced in 1960. Traditional COC's, similar in dosing to what is used today, were introduced in 1967 with Ortho-Novum 1/50[®], which contained 35 mcg EE equivalent. Low-dose pills, often thought of as a new concept, actually originate back to 1973 with Loestrin 1/20[®], which contained 20 mcg of EE/24 hr.

Despite low-dose and traditional pills being available for decades, there is continued debate among practitioners and patients regarding which dose of EE is “better”. This is evident when observing that in 2005, of the two most commonly prescribed oral contraceptive agents, one is a traditional pill (Yasmin[®]), the other a low-dose (Ortho Tri-Cyclen Lo[®]).¹ The objective of this article is to compare traditional oral contraceptive pills to low-dose pills, discussing their respective efficacies and side effect profiles.

Efficacy

Numerous comparative studies have found that efficacy rates of 20 mcg preparations are similar to those of 30/35 mcg preparations. The Pearl Index, an industry standard measure of efficacy that corresponds to number of births per 100 woman years, is similar for both EE strength preparations, ranging from 0.2 – 1.02.²⁻⁸ Overall it appears that pregnancy is prevented at similar rates with both regimens; however, variation in follicle size has been observed.

For a follicle to reach adequate size for ovulation it must reach a diameter of > 16 mm.⁹ Follicles ≥ 10 mm are considered “dominant follicles” and have a greater potential for ovulation.¹⁰ Follicular diameter length has been correlated with the EE content in COC's. Heusden et al. found that women taking 20 mcg EE pills had an 18-27% greater production rate of dominant follicles compared to women taking 30 mcg pills.¹⁰ A recent study involving Triphasil[®] (30-40 mcg EE), Alesse[®] (20 mcg EE), and Ortho Tri-Cyclen[®] (35 mcg EE), found that the low-dose pill, Alesse[®], resulted in statistically significant larger follicle sizes, compared to the other OC agents, in each of the four cycles studied.¹¹ In addition, a study of 209 women compared 30 mcg EE to 20 mcg EE and found follicular development to be twice as frequent in the 20 mcg EE arm and concluded that “reducing the dose to 20 mcg is associated with a significant increase in follicle size”.¹²

Low-dose pills provide acceptable rates of contraception, but may increase a women's ability to produce a dominant follicle. If these regimens are taken exactly as prescribed, follicle size may not be as critical and contraception would sustain. Unfortunately, compliance is an existent burden accompanying oral contraceptives that cannot be overlooked.

Compliance

Compliance is a major concern with all oral contraceptive agents, with irregular use estimated to be as high as 60%.¹³ The 1995 New Survey for Family Growth reported that 15.5% of COC users reported missing one pill and another 13.3% reported missing two or more pills in the past three months.¹⁴ Evidence suggests that missing pills adjacent to the seven day pill-free interval is associated with an increased risk of ovulation regardless of EE dose.^{15,16} However, more follicular activity has been associated with a pill-free interval extension of low-dose

Table 1. Low-dose oral contraceptives

Product ^b	Progestin Component	Manufacturer	Price/Cycle (\$) ^a
<i>20 mcg ethinyl-estradiol</i>			
Levlite [®] (B)	0.1 mg levonorgestrel	Berlex	38
Aviane [®] (G)	0.1 mg levonorgestrel	Barr	33
Alesse [®] (B)	0.1 mg levonorgestrel	Wyeth	38
Lutera [®] (G)	0.1 mg levonorgestrel	Watson	27
Lessina [®] (G)	0.1 mg levonorgestrel	Barr	33
Loestrin 1/20 FE [®] (B)	1 mg norethindrone acetate	Warner Chilcott	55
Microgestin 1/20 FE [®] (G)	1 mg norethindrone acetate	Watson	25
Junel 1/20 FE [®] (G)	1 mg norethindrone acetate	Barr	28
Yaz [®] (B)	3 mg drospirenone	Berlex	50
<i>10/20 mcg ethinyl-estradiol</i>			
Mircette [®] (B)	0.15 mg desogestrel	Duramed/Organon	42
Kariva [®] (G)	0.15 mg desogestrel	Barr	39
<i>25 mcg ethinyl-estradiol</i>			
Cyclessa [®] (B)	0.1/0.125/0.15 mg desogestrel	Barr	43
Velivet [®] (G)	0.1/0.125/0.15 mg desogestrel	Barr	30
Ortho Tri-Cyclen Lo [®] (B)	0.25/0.215/0.18 mg norgestimate	Ortho-McNeil	46

^a Costs as of 12/06, taken as average from: drugstore.com and walgreens.com

^b (B) = brand; (G) = generic

users.¹⁵ In one study, a 10-day pill-free interval resulted in follicles >18 mm in 40% of women on 20 mcg EE while the same follicle size was noted in only 24% of women on 30 mcg EE.¹⁷

The increased follicular activity after missed pills adjacent to the pill-free interval among users of low-dose formulations suggests that the margin of contraceptive safety, or the “degree of forgiveness,” may be decreased in women using these formulations.¹⁵ The transient interruption of traditional regimens in a location other than adjacent to the pill-free interval appears to be less significant.¹⁵ Multiple studies show that missing up to four consecutive pills has not resulted in signs of ovulation.¹⁸ However, similar studies have not been completed using low-dose formulations. Due to the limited evidence on the result of transient interruptions with low-dose pills, the World Health Organization Selected Practice Recommendations for Contraceptive Use (WHOSPR) updated its recommendations to include a more cautious approach when 20 mcg EE or less pills have been missed.¹⁹ These recommendations are summarized in Table 2.

Therefore, decreased compliance, particularly near the pill-free interval, results in increased follicle size and therefore increased risk of ovulation and pregnancy. This risk is increased in women taking low-dose birth control pills compared to traditional pills.

Cycle Control

Lack of cycle control is a major contributor to patient dissatisfaction and a resultant decrease in compliance.²⁰ Estrogen dose clearly affects cycle control, but the severity difference of this effect between low-dose and traditional formulations is ambiguous. In addition to estrogen, individual patient characteristics, progestin dose and type, and the ratio of progestin and estrogen doses can all cause significant variation in cycle control. While inter-individual characteristics may not be easily replicated in a clinical trial, progestin formulations can. Unfortunately, there is limited comparative data involving different estrogen strengths with similar progestin types and doses.

Akerlund et al. compared 150 mcg of desogestrel with both 20 mcg EE and 30 mcg EE. In the

Table 2: Advice for women missing OC's^a

Missed ONE or TWO 30-35 mcg/24 hr pill or Missed ONE 20 mcg/ 24 hr pill	<ul style="list-style-type: none">• She should take a pill as soon as possible and then continue taking pills daily, one each day.• She does not need any additional contraceptive protection
Missed THREE or more 30-35 mcg/ 24 hr pills or Missed TWO or more 20 mcg/ 24 hr pills	<ul style="list-style-type: none">• She should take a pill as soon as possible and then continue taking pills daily, one each day.• She should also use condoms or abstain from sex until she has taken pills for 7 days in a row.• If she missed the pills in the third week, she should finish the pills in her current pack and start a new pack the next day. She should not have a pill-free interval. If the pill-free interval is avoided in this way, she does not need to use emergency contraception.• If she missed the pills in the first week (effectively extending the pill-free interval) and had unprotected sex (in week 1 or in the pill-free interval), she may wish to consider the use of emergency contraception.

^aAdapted from The World Health Organization *Selected Practice Recommendations for Contraceptive Use* (WHOSPR)¹⁹

8,573 cycles analyzed, significantly more irregular bleeding patterns and amenorrhea occurred with the low estrogen formulation.²¹ Another study, which compared 75 mcg of gestodene with both 20 mcg EE and 30 mcg EE, found significantly more spotting among low-dose users, with the largest difference, 22.6% versus 13.8%, occurring during the first cycle of use.²²

Studies involving different progestin components have provided similar results. A 2001 study comparing two low-dose pills with different progestin components and a reference pill of 30 mcg EE, found that the two low-dose pills resulted in considerably more episodes of spotting and breakthrough bleeding than the 30 mcg EE pill.²⁰ The incidence of breakthrough bleeding during the third cycle for the three regimens was 18.4% (EE/LNG 20/100), 39.8% (EE/NET 20/500), and 2.5% (EE/LNG 30/150).²⁰ In a study comparing 20 mcg EE and norethindrone acetate 1 mg to 30 mcg EE and levonorgestrel 150 mcg, the low-dose pill fared worse in frequent, infrequent, and prolonged bleeding incidences.²³

All of these trials show low-dose oral contraceptives to have poorer irregular bleeding outcomes than their traditional dose counterparts. However, different progestin doses and types, the ratio of progestin to estrogen doses, small sample sizes, and/or varying criteria to define bleeding outcomes con-

found most of the comparative trials involving these regimens.²⁴

While a clear picture of the difference between low-dose and traditional pills' relationship to irregular bleeding patterns is not available, it is assumed that low-dose regimens may provide less cycle control for some patients.

Side Effects

Side effect rates raise significant concerns for oral contraceptive users. Estrogenic side effects, such as breast tenderness and nausea, can affect patient satisfaction and compliance. Breast tenderness and nausea are dose-dependent, relating directly to the amount of estrogen each pill contains.²⁵ A study comparing Alesse[®] (20 mcg EE), Mircette[®] (20 mcg EE), and Ortho Tri-Cyclen[®] (35 mcg EE) found that women using the traditional dose pill experienced breast tenderness, nausea, and bloating at an incidence rate 50% higher than their low-dose counterparts.²

Unfortunately, the clear benefit involving a decrease in side effect incidences with low-dose pills stops there. Oral contraceptive use is associated with an increased risk of venous thromboembolism (VTE), stroke, hypertension, and breast cancer. These results may be a product of estrogen dose, progestin dose and type, and inter-individual characteristics. Long-term studies comparing traditional and low-dose regimens with these endpoints have not

been completed. Some studies have compared intermediate markers (i.e. coagulation factors, renin substrates, etc.) and found low-dose pills to have more favorable profiles.²⁴ These studies are preliminary at best, and not predictors of clinical events. Whether a further decrease in estrogen from traditional regimens results in a decrease in these adverse events remains to be seen. However, it can be reasonably hypothesized that a decrease in estrogen will not result in an increase in these outcomes.

Selecting an Appropriate Regimen

The “best” regimen is ideally the one that is the most effective with the least amount of side effects. However, all pills are not created equal for all women, and the needs and concerns of each patient should be fully assessed before determining the most appropriate regimen. For a woman confident with regard to compliance and no history of cycle control problems, a low-dose pill is an acceptable choice.²² For a woman whose primary concern is contraception and who may have issues with compliance, a traditional dose pill may be a better option. A woman with a history of cycle control problems or who experienced such problems with a 20 EE pill, would likely benefit from a 30 mcg EE pill with similar type and strength of progestin.²²

Contraception may not be the most important feature of oral contraceptives for some women. Non-contraceptive benefits of COC’s include reduced acne and hirsutism, reduced pre-menstrual symptoms, decreased incidence of endometrial and ovarian cancers, and reduced incidence of benign breast disease.²⁶ Women primarily interested in non-contraceptive benefits may choose to start with a low-dose formulation.

Conclusion

Combined oral contraceptives have been available for nearly half a century. Today there are over 40 brands on the market. Low-dose pills were introduced over 30 years ago and yet their niche in the marketplace remains ambiguous. Although more research is necessary to determine a difference between traditional and low-dose oral contraceptives, certain facts are becoming evident. Low-dose pills are associated with similar efficacy rates with proper compliance, but an increase in cycle control and irregular bleeding patterns. In addition, certain side effect rates (breast tenderness, nausea, bloating) are

decreased with low-dose pills, while the effect of decreased estrogen on other negative outcomes (VTE, stroke, hypertension, etc.) remains unclear. With no guidelines currently available, the most appropriate regimen varies with each patient and should be determined on a case-by-case basis.

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