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MANAGEMENT OF ACNE VULGARIS: A REVIEW

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Acne vulgaris is a common skin disorder caused by abnormal hyperkeratinization and overproduction of sebum by the sebaceous gland. Acne first presents early in adolescence and often continues into early adulthood, negatively affecting quality of life. This article will review the current treatment options for acne vulgaris.[1]

EPIDEMIOLOGY

Acne may be psychologically impacting in late adolescence, leading to depression and diminished quality of life. In the United States, acne affects about 40-50 million people[1] – impacting nearly 80% of the population between 12-25 years – without gender, ethnicity or race prevalence differences. The onset of acne vulgaris varies within age groups, but is more prevalent during the onset of puberty, and can continue to be a problem throughout early adulthood.[2]

ETIOLOGY & PATHOPHYSIOLOGY

The origin of acne vulgaris is complex, but at least four primary factors are associated with its development, including increased sebum production, sloughing of keratinocytes, bacterial growth and colonization, and inflammation and immune system response. At puberty, stimulation of androgens, especially testosterone, is enhanced. Testosterone and its active metabolites stimulate sebaceous gland activity, leading to an increase in sebum production. When hyperkeratinization occurs during the natural sloughing process, sebum mixes with clumped keratinocytes. This clumping leads to plugging of the follicle, thus widening the follicle and producing a favorable environment for bacteria, such as *Propionibacterium acnes*. Subsequently, primary acne lesions form, appearing as blackheads, also known as open comedos. After development of a blackhead, trauma or inflammation to the follicles may ultimately lead to the formation of closed comedos, or whiteheads.[1,3] A variety of factors increase the risk for acne vulgaris (Table 1).

TREATMENT OF ACNE

Various therapies are available for the treatment of acne vulgaris, including topical and oral agents Preferred therapies differ based on the severity of disease presentation.

Mild-to-Moderate Acne: Topical Antibiotics

Topical antibiotics including erythromycin and clindamycin, are effective and well tolerated for the treatment of acne vulgaris. However, because antibiotics may potentially decrease sensitivity of *P. acnes*, the use of these agents should be limited.[4] Erythromycin is used alone for inflammatory acne or in combination with zinc, which helps the antibiotic penetrate into the pilosebaceous units. Clindamycin inhibits *P. acnes* and

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Table 1: Risk factors for acne vulgaris.

Environmental Factors:
- High-humidity
- Prolonged sweating
- Increase in skin hydration
- Exposure to dirt or vaporized cooking oil or certain chemicals like petroleum derivatives

Cosmetic Use:
- Moisturizers
- Tanning oils
- Cocoa butter

Hormonal Factors:
- Menarche
- High-androgenic progestin birth control

Emotional Factors:
- Severe/prolonged period of stress

Physical Factors:
- Occlusive clothing
- Headbands
- Helmets
- Friction-producing devices

Medication Use:
- Phenytoin
- Isoniazid
- Phenobarbital
- Lithium
- Ethonamide
- Steroids
- Azathioprine
- Quinine
- Rifampin

Adapted from Haider A, et. al.[3]

possesses comedolytic and anti-inflammatory properties.[1]

Topical antimicrobial combination therapy is more effective than monotherapy.[1,4] A randomized, parallel, vehicle-controlled trial by Lookingbill and colleagues evaluated 334 patients over an 11-week once-nightly preparation study. Evaluation was performed on weeks 2, 5, 8 and 11 for lesion counts, global response rate and irritant effects of clindamycin plus benzoyl peroxide gel, benzoyl peroxide alone, clindamycin alone or vehicle gel.[5] The combination of clindamycin/ benzoyl peroxide significantly improved patient global response and reduced inflammatory and non-inflammatory response compared to clindamycin alone, benzoyl peroxide alone, or the vehicle gel. Monotherapy with clindamycin or benzoyl peroxide compared to the vehicle gel resulted in significant improvement in patient global response and a reduction in inflammatory and non-inflammatory response. All of the treatment options were well tolerated.[5] Table 2 summarizes the clinical studies of various products used to treat acne vulgaris, including topical antibiotics.

Mild-to-moderate Acne: Topical Retinoids

The available topical retinoids used for acne vulgaris include tretinoin (Retin-A®), adapalene (Differin®) and tazarotene (Tazorac®) (Table 3). These agents work by reducing obstruction within the follicle.[4,6,7] Such products are considered first-line for the treatment of mild-to-moderate inflammatory acne and comedonal acne.[2] Additionally, these agents are preferred for maintenance therapy of acne in order to preserve the use of antibiotics.[4] Topical retinoids are most effective when used in combination with topical antibiotics or benzoyl peroxide (Brevoxyle ®).[1]

A meta-analysis by Leyden and colleagues, evaluating topical tazarotene in mild to moderate acne, found that tazarotene was well tolerated and effective for the treatment of acne vulgaris, regardless of patient-specific factors, including acne severity, skin type, sex or ethnicity. Six comparative, multicenter, double-blind, randomized studies of monotherapy with tazarotene 0.1% gel or cream were analyzed, encompassing 468 patients who exhibited moderate to complete clearing at 12 weeks. Both inflammatory and non -inflammatory lesion counts declined substantially with both formulations over the treatment period. Furthermore, both formulations were well-tolerated.[8] In a 3-way retrospective, investigator blinded, photographic review, investigators evaluated the efficacy of tazarotene 0.1% gel, adapalene 0.1% gel, tretinoin 0.1% microsponge, and tretinoin 0.025% gel for the treatment of inflammatory acne. The authors concluded that all formulations showed significant clinical improvements compared to tazarotene 0.1% cream (vehicle).[7]

Mild-to-moderate Acne: Combination therapy

Recent guidelines suggest that combination therapy with topical retinoids and antimicrobial agents achieves significantly greater and faster clearing of acne compared with antimicrobial therapy alone.[2] Combination therapies utilize agents with complimentary mechanisms of action to target multiple etiological factors simultaneously.[2,8]

Gollnick and colleagues recently conducted a randomized, double-blind, placebo-controlled study to

Table 2. Clinical studies summary.

STUDY	METHODS	STUDY GROUPS	RESULTS
Lookingbill, et al.[3] (1997)	11-week, RCT, PL (n=334)	Study groups: • Clindamycin + BPO gel • BPO gel • Clindamycin gel • Placebo (vehicle gel)	• Clindamycin + BPO showed SS (P<0.001) good/excellent PGR, ß in inflammatory and non-inflammatory response and was significantly superiority to clindamycin, BPO, or vehicle gel alone. • Clindamycin and BPO alone were SS (P<0.001) vs. vehicle gel in PGR, ß in inflammatory and non-inflammatory response.
Leyden, et al.[9] (2004) Meta-analysis	6-comparative MC, DB, R studies evaluated 468 patients with mild-moderate acne	• Tazarotene 0.1% gel • Tazarotene 0.1% cream	Both groups showed: • Moderate clearing after 12 weeks • Statistical ß in inflammatory and non-inflammatory lesions • Well tolerated
Leyden, et al.[5] (2005)	3-way RS, IB, photographic review evaluating efficacy of topical retinoids	• Tazarotene 0.1% gel • Adapalene 0.1% gel • Tretinoin 0.1% microsponge • Tretinoin 0.025% gel • Tazarotene 0.1% cream	• All formulations showed significant clinical improvements in inflammatory acne vs. to vehicle.
Gollnick et al.[8] (2009)	DB, RCT evaluating safety and efficacy	• Adapalene 0.1% + BPO 2.5% gel • Adapalene 0.1% • Adapalene 2.5% • BPO 2.5% • Vehicle gel	• Adapelene + BPO was SS more effective (P<0.001) at weeks 8, 12, and end-point than monotherapy and SS more effective (P<0.05) at weeks 2 and 4 than vehicle-only. • A significant difference in lesion counts from baseline as early as the 1st week. • Equal tolerability in all groups. • More AEs with adapalene-BPO early in therapy, but only transient.
Krunic, et al.[12] (2008)	27 females 18-43 with severe papular or NC facial acne	• Spironolactone + 30mcg EE/3mg DRSP	• 85% subjects had complete clearing of lesions or excellent improvement • 7.4% had mild improvement • 7.4% had no improvement.
Palombo-Kinne, et al.[13] (2009)	MN, MC, 3-arm, DB, RCT, women 16-45 with mild-to-moderate facial acne	Completed 6 cycles of either: • EE/DNG, • EE)/ CPA, or • PL	• EE/DNG was superior to PL and non-inferior to EE/CPA (P<0.05). • Rates of ß in inflammatory lesions were -65.6+/-29.9% for EE/DNG, 64.6+/-31.2% for EE/CPA and 49.4+/-41.0% for PL. • Percentages of pts with improvement of facial acne were 91.9% for EE/DNG, 90.2% for EE/CPA and 76.2% for PL.
Jones, et al.[14] (1983)	RCT, 76 pts with severe acne	• Isotretinoin 0.1mg/kg/day to 0.5mg/kg/day	• 80% ß in total acne after 4 months. • 89% ß in total lesions when a 1.0mg/kg/day dose was used.

RCT = randomized controlled trial; MN = multinational; MC = multicenter; DB = double-blind; RS = retrospective; IB = investigator-blind; R = randomized; SS = statistically significant; PGR = patient global response; NC = nodulocytic; y/o = years old; PL = Placebo; Pts = Patients.

assess the safety and efficacy of adapalene 0.1% + benzoyl peroxide (BPO) 2.5% combination gel and 0.1% adapalene, 2.5% BPO, or a vehicle gel. The authors reported that combination therapy was more effective (P<0.001) at weeks 8 and 12, and at study end compared with BPO monotherapy and a vehicle gel. Moreover, combination therapy was more effective (P<0.05) at weeks 2 and 4 compaed with vehicle-only. A significant difference in lesion counts from baseline was reported as early as the 1st week. Adverse effects were more prevalent in the early phase of treatment with combination therapy, but these effects were transient. This study showed that combination therapy was significantly better, synergistically efficacious with a faster onset, and had an equivalent safety profile when compared to the monotherapies.[8]

Mild-to-Moderate Acne: Hormonal Therapy

Hormonal therapy produces anti-androgen effects, which leads to a decrease in testosterone circulating in the body. Consequently, sebaceous gland stimulation is prevented, reducing sebum production.[3,10] FDA-approved hormonal therapies consist of oral contraceptive agents that contain norgestimate with ethinyl estradiol (Ortho-Tri-Cyclen®) and norethindrone acetate with ethinyl estrodial (Estrostep®), as well as the anti-androgenic agent, spironolactone (Table 4).[4]

Anti-androgens, such as spironolactone or cypro-

Table 3. Topical agents for the treatment of acne vulgaris.[11,15]

DRUG	BRANDS	MECHANISM	STRENGTH/DOSES	SIDE EFFECTS	COST
Clindamycin (antibiotic)	Cleocin T, Clindagel® Clindesse®, Clinda-derm®, Evoclin®	Inhibits 50s ribosomal subunit of bacteria, which inhibits protein synthesis	1% (cream, solution, pads) Any topical applied on affected area twice daily.	Pruritis, acute generalized exanthematous pustulosis, burning, xerosis, erythema, oiliness, peeling.	1% 60gm: AVP = $48.67
Erythromycin (antibiotic)	Akne Mycin®, E-Mycin®, EMGEL®, Ery-Pad®, Ery-gelR®	Inhibits 50s ribosomal subunit of bacteria, which inhibits protein synthesis	1.5% - 2% (solution, gel, ointment) Any topical applied on affected area twice daily.	Pruritis, acute generalized exanthematous pustulosis, nausea, vomiting, diarrhea, and anorexia.	2% 60gm: Gel = $ 34.99 Soln = $ 14.99
Sulfacetamide (antibiotic)	Cetamide®, Klaron®, Ovace®, RE-10 wash®, Rosula NS®, Seb-Prev®	Inhibits bacterial DHFS, interfering with FA synthesis, an essential component for bacterial development	10% lotion Apply on affected area twice daily.	Hypersensitivity to sulfacetamide, which may progress to lupus like syndrome.	RE-10 Wash: $87.99
Dapsone (antibiotic)	Aczone®	Mechanism similar to sulfacetamide, but for dermatological disorder; possible immunomodulator	5% gel Apply on affected area twice daily.	Photosensitivity (Most problems are seen in leprosy patients)	60gm tube: $294.99
Adapelene	Differin®	Binds specific nuclear RAR, penetrating deep into hair follicles, modulating cell differentiation and keratinization. Also has potent AI and comedolytic properties	0.1% (cream or gel) & 0.3% (gel) Apply to affected areas once daily before bedtime.	Erythema, burning, xerosis, skin irritation, photosensitivity, pruritus.	45gm tube (0.1%, 0.3%): $203.99
Azelaic Acid	Azelex®, Finacea® Finacea Plus®, Finevin®	Exact mechanism unknown: inhibits microbial protein synthesis; BS at lower doses; BC at higher doses. Also direct AI and AK effects	15%-20% (gel or cream) Apply to affected areas twice daily.	Contact dermatitis, erythema, hypertrichosis, infection, pruritus, rash (unspecified), skin hypopigmentation, skin irritation, xerosis.	Finacea 50gm: $140.99 Azelex 50gm: $188.99 (NO GENERIC)
Benzoyl Peroxide	Acne-10®, Acne-5® Acneclear®, Benoxyl ® Benoxyl®, Benprox®, Benzac®, Benzac®, Benzagel®, Benziq®, Brevoxyl®, ClearPlex®, Desquam EX®, Fostex®, Inova® Lavoclen®, others	Releases FR oxygen species oxidizes bacterial proteins. Also keratolytic activity	2.5% to 10% (creams, gels or lotions) Apply once daily and gradually increase to four times daily.	Contact dermitis, erythema, pruritus, rash (nonspecific), skin irritation, xerosis	60gm gel tube: BPO-10 - $29.09 BPO-5 - $22.89 297gm lotion: BPO 4% - $55.59 BPO 8% - $57.59
Tazoretene	Avage®, Tazorac®	Exact mechanism unknown; Bind specific nuclear RAR, and exerts effects on keratinocyte differentiation, proliferation, and inflammation.	0.1% (creams or gel) Apply a thin film on the affected area in the evening.	Desquamation, burning/stinging, xerosis, erythema, pruritus, skin irritation, skin pain, fissuring, localized edema, and skin discoloration.	60gm tube cream: 0.05% - $272.99 0.1% - $291.99 100gm tube gel: 0.05% - $451.99 0.1% - $383.99
Trentinoin	Altinac®, Atralin® Avita®, Renova®, Retin-A®, Trentin-X®, Vesanoid®	Binds to RAR, modifying gene expression, thus affecting protein synthesis, epithelial cell growth and differentiation. Also has AK effects.	0.025%, 0.04%, 0.05%, or 0.1% (cream, liquid, gel) Apply to affected area once daily at bedtime.	Burning, stinging, xerosis, peeling, erythema, and pruritus. Also, skin hyper- or hypo-pigmentation, photosensitivity.	45gm tube: 0.01% gel - $96.59 0.025% cream - $52.99 0.025% gel - $85.99 0.05% cream - $101.99 0.1% cream - $85.59

DHFS = dihydrofolate synthetase; FR = free radical; RAR = retinoic acid receptor; BS = bacteriostatic; BC = bacteriocidal; AI = anti-inflammatory; AK = anti-keratinization; FA = folic acid; AVP = average variable price

Table 4. Oral agents for the treatment of acne vulgaris.[11,15]

DRUG	BRANDS	MECHANISM	STRENGTH/DOSES	SIDE EFFECTS	COST
Drospirenone; Ethinyl Estradiol	Ocella®, Yasmin®, Yaz-28®	Some have less/no androgenic activity, thus preventing TT production, and are less likely to stimulate/aggravate sebaceous glands.	Prolonged use (> 2 -4 months) needed for acne resolution.	Menstrual irregularity, breakthrough bleeding, spotting in the 1st 3 months, migraines, venous thrombosis embolism, hypertension, vaginal discharge, vaginal irritation, mood/personality changes, ocular disorders, Melasma, photosensitivity, bleeding of the gums, rash, urticaria, erythema, alopecia, hirsutism, can exacerbate acne vulgaris	Yaz/Yasmin: $74.59 Ocella: $59.99 (G) 28 tablets (ALL) MonoNessa®: $27.99 Ortho-Tri-Cyclen Lo®: $62.59 (B) Tri-Lo-Sprintec®: $54.99 (G) Ortho-Tri-Cyclen ®: $47.39 (B) Tri-Sprintec®: $31.39 (G) Trinessa®: $47.39 (G) Ortho-Cyclen®: $48.49 Sprintec®: $27.99
Ethinyl Estradiol; Norgestimate	MonoNessa®, Ortho Tri-Cyclen Lo®, Ortho-Cyclen®, Ortho Tri-Cylcen®, Sprintec®, Tri-Sprintec®, Previfem®, Tri-Previfem®, Trinessa®				
Isotretinoin	Accutane®, Amnesteem®, Clavaris®, Sotret®	Shows reversible inhibition of sebum production by reduction in sebaceous glands, and possible inhibition of follicular keratinization. Also might have AI effects.	0.5-1 mg/kg/day in two divided doses for 15-20 weeks.	Cheilitis, xerosis, xerostomia, epistaxis, peeling, pruritus, acneiform rash, alopecia, eczema, flushing, hirsutism, impaired wound healing, infection, photosensitivity, seborrhea, skin fragility, skin hyper-, hypopigmentation, urticaria.	40mg AVP (30 tablets): $272.49 (ALL GENERICS) Accutane (B) 40mg (30 tablets): $849.99
Spironolactone	Aldactone®, Spirono®	Acts as an ARA, competitively inhibiting TT, a steroid that triggers secretion of oil by sebum glands, leading to acne. Inhibition leads to decrease in sebum production.	50-200 mg/day	Cardiac arrhythmias, hyperkalemia, gynecomastia, libido decrease, menstrual irregularity, post-menopausal bleeding, breast tenderness, hirsutism, amenorrhea	25mg (30 tablets): $11.19 (FOR GENERIC)
Doxycycline (antibiotic)	Adoxa®, Adoxa, Pack®, Alodox®, Atridox®, Avidoxy®, Doxy®, Doxy 100®, Oracea®, Oraxyl® Periostat®, Vibra-Tabs®, Vibramycin®	Reversibly binds to 30s subunit of bacteria, which blocks mRNA and tRNA function, thus blocking protein synthesis.	100 mg twice daily on day 1, then 100mg once daily	Diarrhea, nausea, vomiting, epigastric distress, anorexia, esophagitis, vaginal candidiasis, photosensitivity, rashes, nail discoloration, AGEP, neutropenia and eosinophilia	50mg (30 tablets): $35.79 (G)
Minocycline (antibiotic)	Arestin®, Cleeravue-M®, Dynacin® Minocin®, Myrac®, Solodyn®		1mg/kg once daily given for 12 weeks	AA, anorexia, dyspepsia, enterocolitis, glossitis, N/V/D, pancreatitis, pseudomembranous colitis, and stomatitis, asthma exacerbation, cough, dyspnea, bronchospasm, pneumonitis, bone discoloration, photosensitivity, rash, nail discoloration alopecia, vaginal, rectal, or oral candidiasis,	50mg (30 tablets): $97.59 (G)

ARA = androgen receptor antagonist; RAR = retinoic acid receptor; TT = testosterone; AA = abdominal pain; N/V/D = nausea, vomiting, diarrhea; AGEP = acute generalized exanthematous pustulosis; AVP = average variable price; G = generic; B = brand

terone, and oral estrogens, such as ethinyl estradiol, decrease androgen levels in patients with acne. Krunic et. al., evaluated the safety and efficacy of daily sprionolactone (SL) 100 mg ,ethinyl estradiol 30 mcg, and drospirenone (EE/DRSP; Yasmin®) 3 mg. The study found that 85% of subjects had complete clearing of acne lesions or excellent improvement, 7.4% had mild improvement, and 7.4% had no improvement. No significant increase in serum potassium or other side effects were observed in any subjects. The authors concluded that EE/DRSP combination therapy and SL 100 mg daily was well tolerated and efficacious in the treatment of severe papular and nondulocystic acne in women.[12]

In a multinational, multicenter, three-arm, double-blind, randomized trial, Palombo-Kinne evaluated healthy women between the age of 16 and 45 with mild to moderate facial acne. Participants were randomly assigned to ethinylestradiol (EE)/dienogest (DNG), ethinylestradiol (EE)/cyproterone (CPA) or placebo for six cycles. The primary efficacy variables were the percent change from baseline to cycle 6 in inflammation and total lesion count and the percentage of patients with improvement in acne evaluated by the Investigator Global Assessment. The study found that EE/DNG was superior to placebo and non-inferior to EE/CPA. The rates of reduction (± SD) in inflammatory lesions were -65.6+/-29.9% for EE/DNG, -64.6+/-31.2% for EE/CPA and -49.4+/-41.0% for placebo. The percentages of patients with improvement of facial acne were 91.9% for EE/DNG, 90.2% for EE/CPA and 76.2% for placebo. The authors concluded that EE/DNG was superior to placebo and as effective as EE/CPA for treatment of mild to moderate acne.[13]

Severe Acne: Oral Isotretinoin

Isotretinoin (Accutane®) is a naturally occurring metabolite of Vitamin A, and is indicated for the treatment of severe acne. Isotretinoin works by reducing the size of the sebaceous gland, suppressing sebum production, and normalizing follicular epithelial desquamation (Table 4).[14] Several studies show isotretinoin to be effective in severe acne. In a randomized controlled trial with 76 patients, isotretinoin showed an 80% reduction in total acne after 4 months. Treatment doses ranged from 0.1mg/kg/day to 0.5mg/kg/day. An 89% reduction in total lesions was observed at the 1.0mg/kg/day dose.[10,14] Although the drug is effective for severe acne, reported side effects may be severe, including inflammation of the lips, which is dose related. In addition, xerosis, xerostomia, epitaxis, peeling, pruritus, nausea/vomiting, altered lipid profiles, and most importantly, teratogenesis may occur with any amount of isotretinoin ingestion.[10] Because of the teratogenicity, men and women of child-bearing age are asked to register and comply with the FDA approved iPLEDGE program. This program is a risk management program that prevents isotretinoin exposure to the fetus.

SUMMARY

Many well-tolerated and effective options are available for the treatment of acne vulgaris, depending on the type and severity of disease. Topical retinoids, antibiotics and BPO are effective for mild-to-moderate acne, while oral isotretinoin and hormonal therapy are effective for more severe cases. In addition, combination therapy with clindamycin and BPO is more effective than treatment with either alone. Management of this common dermatologic disorder may contribute to a better quality of life.

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REFERENCES

1. Pharmacotherapy: A Pathophysiological Approach. Joseph T. DiPiro, Robert L. Talbert, Gary C. Yee, Gary R. Matzke, Barbara G. Wells, L. Michael Posey (Eds). 7th edition. Chapter 100. Acne Vulgaris: Treatment: Acne Vulgaris. Accesspharmacy. http://www.accesspharmacy.com/content.aspx?aID=3212123
2. Thiboutot D, Gollnick H. New insight into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol 2009;60:S1-50.
3. Haider A, Shaw J. Treatment of Acne Vulgaris. JAMA:2004;292 (6):726-35.
4. Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007;56 (4):651-63.
5. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindaymycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double blind investigations. J Am Acad Dermatol 1997;37:590-5.
6. Fox Lindy P, Merk Hans F, Bickers David R. Chapter 62: Dermatological Pharmacology. Laurence L. Brunton, John S. Lazo, Keith L. Parker (Eds): Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e: http://www.accesspharmacy.com/content.aspx?aID=959337
7. Leyden JJ, Shalita A, Thiboutot D, et al. Topical retinoids in inflammatory acne: A retrospective, investigator-blinded, vehicle-controlled, photographic assessment. Clin Ther 2005;27:216-24.
8. Gollnick HPM, Draelos Z, Glenn MJ, et al. Adapelene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind controlled study in 1670 patients, Br J Dermatol 2009 [Epub ahead of print].
9. Leyden JJ. Meta-analysis of the topical tazarotene in the treatment in the treatment of the mild to moderate acne. Cutis 2004;74(supp 4):9-15.
10. George R., Clarke S, et al. Hormonal Therapy in Acne. Semin Cutan Med Surg 2008:27(3):188-96.
11. Gold Standard, Inc. Clinical Pharmacology [database online].

Available: http://www.clinicalpharmacology.com. Accessed: July 15, 2009.
12. Krunic A, Ciurea A, Scheman A, et al. Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone. J Am Acad Dermatol 2008;58:60-2.
13. Paloma-Kinne E, Schellschmidt I, Schumacher U, et al. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. Contraception 2009 ;79(4):282-9.
14. Jones DH, King K, Miller AJ, et al. A dose response study of 13-cis retinoic acid in acne vulgaris. Br J Dermatol 1983;108:333-43.
15. Lexi-Comp Online™ , 2009. Accessed: July 15, 2009. Available: http://www.crlonline.com/crlsql/servlet/crlonline.

DRONEDARONE: A NEW TREATMENT OPTION FOR ATRIAL FIBRILLATION

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting approximately 2.2 million people in the US.[1] AF is prevalent in <1% of adults younger than 55 and approaches 10% in those older than 80.[2] AF results in hemodynamic and thromboembolic complications, and increases the rate of ischemic stroke 5 fold.[1,3] Hospitalization rates due to AF have increased by 66% during the past 20 years resulting in a significant public health burden. This cost will continue to rise due to an aging population.[3,4] One of every six strokes occurs in a patient with AF with mortality rates doubled compared to patients in sinus rhythm.

Treatment for AF consists of ventricular rate control or sinus rhythm control with concomitant anticoagulation therapy. Use of long term antiarrhythmic therapy may be needed in the majority of patients due to the high rate of recurrence after electrical or pharmacological cardioversion. Antiarrhythmic drugs also may be started when symptoms are not suppressed with rate control therapy alone. But the choice of antiarrhythmic agent must take into account the safety profile of the drug as well as the underlying heart disease of the patient.[3]

Amiodarone, a class III antiarrhythmic drug, is effective and commonly used for maintenance of sinus rhythm. In the AFFIRM trial, 67% of patients in the rhythm control group were started on amiodarone or sotalol; and at the end of the study 66% of the patients had tried amiodarone at least once.[5] An advantage of amiodarone is the low poarrhythmic risk of in left ventricular (LV) hypertrophy, heart failure (HF), coronary artery disease, and post myocardial infarction.[3] However, this agent is limited by extra-cardiac toxicities including pulmonary fibrosis, hepatic and thyroid dysfunction, neurological disorders, blue-gray skin discoloration, and corneal deposits. In addition, amiodarone has a complicated dosing schedule and interacts with some cardiovascular (CV) agents including warfarin and digoxin.[3,6] Dronedarone (Multaq®) is an amiodarone analogue manufactured by Sanofi-Aventis and recently approved by the FDA in July 2009. The structure of dronedarone differs from amiodarone by the absence of iodine and the presence of a methanesulfonyl group that decreases lipophilicity. These changes were intended to reduce accumulation in tissues to prevent thyroid and other peripheral adverse effects.[7] This article will review the efficacy, safety and tolerability of dronedarone for maintenance of sinus rhythm in AF.

PHARMACOLOGY AND PHARMACOKINETICS (PK)

Dronedarone is a benzofuran derivative that has electrophysiological properties of all Vaughan-Williams antiarrhythmic drug classes. Specifically, dronedarone blocks sodium and calcium channels, demonstrates noncompetitive antiadrenergic actions and prolongs the action potential and refractory periods.[8] Oral dronedarone prolongs the PR and QTc interval in a dose-dependent manner. Heart rate is not affected by oral administration of 400 mg twice daily and is reduced by ~4 beats/min with 800 mg twice daily.[9]

Dronedarone undergoes extensive first-pass metabolism and has a low bioavailability that is increased by food. A 2-fold increase in dose results in an approximate 2.5- to 3.0- fold increase in Cmax and AUC, indicating nonlinear PK. The main active circulating metabolite is formed by N-debutylation. This N-debutyl metabolite has one-tenth to one-third the potency of dronedarone. Time to peak plasma concentration of dronedarone and its primary metabolite is 3 to 6 hours under fed conditions. Dronedarone reaches steady-state concentrations after 4 to 8 days of oral administration of 400 mg twice daily. Steady-state Cmax and AUC are similar for both parent and active metabolite. Dronedarone moderately inhibits CYP3A and CYP2D6. [10]

Females have an approximate 30% greater expo-

sure to dronedarone than males. In a cross study, Japanese men showed a 2-fold increase in dronedarone levels compared to Caucasian men after a single dose of 400 mg. Patients > 65 years of age have a 23% higher exposure than younger patients. Dronedarone exposure is increased by 30% and the N-debutyl metabolite is decreased by about 50% in patients with moderate hepatic impairment. Dronedarone's PK have not been studied in individuals with severe hepatic impairment. No significant PK differences were observed in patients with mild to severe renal insufficiency relative to patients with normal renal function.[10] In animal studies, dronedarone distributes widely throughout the body, crosses the placenta and blood brain barrier, and is excreted into breast milk.[9] These PK properties differ significantly from those of amiodarone (Table 1).

CLINICAL TRIALS

ANDROMEDA

ANDROMEDA was a randomized, double-blind, placebo-control, parallel-group, multicenter trial conducted to test the hypothesis that dronedarone 400 mg twice daily could decrease hospitalization and sudden cardiac death caused by arrhythmia in patients with HF.[11] Study participants were hospitalized patients with new or decompensated HF who had had symptoms of NYHA class III/IV HF or paroxysmal nocturnal dyspnea within the month before hospitalization. The primary end point was death from any cause or hospitalization from worsening HF. The study was originally planned for 2 years, but was prematurely stopped at 7 months (January 2003) due to excess mortality in patients assigned to dronedarone. Participants were followed for 6 months after discontinuation of the study drug.

In the course of a median follow up of 2 months, a total of 25 patients (8.1%) died in the dronedarone group and 12 patients (3.8%) died in the placebo group. In the dronedarone arm, 24 out of the 25 deaths were caused by CV events. Ten of these CV deaths were caused by worsening HF. In the placebo arm, 9 out of the 12 deaths were caused by CV events. Two of these deaths were from worsening HF. The number of patients having a first hospitalization for an acute CV event was more common in the dronedarone group (71 patients) compared to placebo (50 patients). Overall, rates of hospitalization due to any CV cause were higher in the dronedarone group. The main cause of these hospitalizations was worsening HF (35 patients taking dronedarone vs. 30 taking placebo). The only significant laboratory adverse event more common with dronedarone was an increase in serum creatinine. This increase in serum creatinine was observed immediately after the start of therapy and returned to baseline after discontinuation of dronedarone.

The authors concluded that dronedarone should not be used in patients with HF and LV systolic dysfunction, and that further studies were needed to analyze the effect of the drug on renal function (Table 2).

EURIDIS/ADONIS

EURIDIS/ADONIS were two identical, randomized, double-blind, parallel-group, placebo-controlled, multinational trials comparing dronedarone 400 mg twice daily with placebo in patients with at least one episode of AF or atrial flutter (AFL), on sinus rhythm at time of randomization, and without NYHA class III/IV HF.[12] EURIDIS was conducted in Europe and ADONIS in America, Africa and Australia. The primary endpoint was time to first recurrence of AF/AFL.

The combined results of both trials favored dronedarone: time to recurrence was 116 days with dronedarone vs. 53 days with placebo (HR=0.75, p=0.001).

Table 1. Pharmacokinetic of dronedarone and amiodarone

PROPERTY	DRONEDARONE	AMIODARONE
Oral bioavailability	15% with high fat meal; 4% without meals	35%-65%
Protein binding	>98% (mainly albumin)	~96%
V_d (steady state)	1400 L (IV)	4936 L
Metabolism	CYP3A4 (>84%)	CYP3A4 and CYP2C8
Principal active metabolite	N-debutyl metabolite	N-desethylamiodarone
Excretion	Urine: ~6% mainly as metabolites Feces:~84% mainly as metabolites	Urine: negligible Bile: primary
Elimination half life	13-19 hours	15-142 days
Effect on CYP450 and P-gp	CYP3A and CYP2D6 moderate inhibitor; potential P-gp inhibitor	CYP3A4, CYP1A2, CYP2C9, CYP2D6 inhibitor

V_d = volume of distribution; P-gp = P-glycoprotein

Table 2. Summary of efficacy and safety trials of dronedarone

TRIAL	PATIENTS	DESIGN	PRIMARY ENDPOINT (PE)	RESULTS
EURIDIS/ADONIS[12] (2007) n=1237	Paroxysmal or Persistent AF/ AFL	DB RCT DRO 400mg BID (n=828) vs. PCB (n=409) Follow up: 12 mo	Time to 1st recurrence of AF/AFL	EURIDIS PE: 96 days (DRO) vs. 41 days (PCB), p=0.01 Recurrence at 12 mo: 67.1%(DRO) vs. 77.5%(PCB) HR*=0.78, p=0.01 ADONIS PE: 158 days (DRO) vs. 59 days (PCB), p=0.002 Recurrence at 12 mo: 61.1%(DRO) vs. 72.8% (PCB) HR*=0.73, p=0.002
ANDROMEDA[11] (2008) n=627	Hospitalized patients with new or worsening HF, with NYHA class III/IV HF or paroxysmal nocturnal dyspnea	DB RCT DRO 400mg BID (n=310) vs PCB (n=317) Median follow up: 2 mo	Death from any cause or hospitalization for worsening HF	PE: 53 events (DRO) vs. 40 (PCB) HR*=1.38 p=0.12 Death: 8.1% (DRO) vs. 3.8% (PCB) HR*=2.13%, p=0.03 1st CV Hospitalization 71 Pts (DRO) vs. 50 Pts (PCB) p=0.02, worsening HF was main reason 35 Pts (DRO) vs. 30 Pts (PCB)
ATHENA[7] (2009) n= 4628	Paroxysmal or persistent AF/AFL with recent episode and risk factors	DB RCT DRO 400mg BID vs. PCB Mean follow up: 21±5 mo	First hospitalization due to CV events or death from any cause	PE: 31.9% (DRO) vs. 39.4% (PCB) HR*= 0.76 p<0.001 1st CV hospitalization: 29.3% (DRO) vs. 36.9% (PCB) HR*=0.74 p<0.001, driven by reduction in hospitalization for AF & ACS All-cause mortality: 5% (DRO) vs. 6% (PCB) HR*=0.84 p=0.18 CV mortality: 2.7% (DRO) vs. 3.9% (PCB) HR*=0.71 p<0.03 mainly driven by reduction in death from cardiac arrhythmia
DIONYSOS[13] (pending) n=504		DRO 400 mg BID vs. AMIO 600 mg daily X 28 days then 200 mg daily Duration: mean 7 months	Recurrence of AF or discontinuation of the study drug because of lack of efficacy or intolerance	PE: 73.9% (DRO) vs. 55.3% (AMIO) p<0.001 AF recurrence: 36.5%(DRO) vs. 24.3%(AMIO) Premature discontinuation: 26 patients (DRO) vs. 34 (AMIO).

*HR are for dronedarone group

ACS=acute coronary syndromes; ADONIS=American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm; AF=atrial fibrillation; AFL=atrial flutter; AMIO=amiodarone; ANDROMEDA=Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease; ATHENA=A Placebo-Controlled, Double Blind Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg Bid for the Prevention of Cardiovascular Hospitalization or Death from any cause in Patients with AF/AFL; CV=cardiovascular; DB=double blind; DIONYSOS=The Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with AF; DRO=dronedarone; EURIDIS=European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm; HF=heart failure; NYHA=New York Heart Association; PCB=placebo Pts=patients; RCT randomized-placebo-control trial.

The rates of symptomatic first recurrence were 37.7% in the dronedarone group vs. 46.0% in the placebo group (p<0.001). In addition, the ventricular rate (bpm) during recurrence was lower with dronedarone (117.5 ± 29.1 and 116.6 ± 31.9, in EURIDIS and ADONIS, respectively) compared to placebo (102.3 ± 24.7 and 104.6 ± 27.1). Rates of hospitalization or death at 12 months were 22.8% with dronedarone and 30.9% with placebo. More cases of hyperthyroidism and increase in creatinine concentration were seen with dronedarone.

The authors concluded that dronedarone was better at reducing rates of first recurrence and symptomatic recurrence at 12 months without significant prolongation of the QT or QTc interval.

ATHENA

ATHENA was a randomized, double-blind, placebo-controlled, parallel-arm, multinational trial that assessed the efficacy of dronedarone in the prevention of CV hospitalization or death from any cause in patients with AF/AFL.[7] Patients included in the study

had a recent episode (within 6 months) of paroxysmal or persistent AF/AFL and at least one of the following risk factor: age ≥ 70, diabetes, taking ≥ 2 antihypertensive medications, previous stroke/TIA/systemic emboli, left atrial (LA) diameter ≥ 50 mm, left ventricular ejection fraction (LVEF) ≤ 40%. The study excluded patients with recent HF decompensation and NYHA class IV HF. Patients were randomized to receive either placebo or dronedarone 400 mg twice daily. Approximately 25% of patients entered the study while on AF/AFL (patients not on sinus rhythm at enrollment were expected to be cardioverted); ~21% had NYHA classII/III HF; and ~12% had LVEF < 45%. The most common underlying CV disease was hypertension (~85%) and structural heart disease was present in ~60% of patients. The primary endpoint was first hospitalization due to CV events or death from any cause, including death from cardiac arrhythmia, non-arrhythmic cardiac causes, noncardiac vascular causes, and non-CV causes.

The primary endpoint was reached by 734 (31.9%) patients in the dronedarone group vs. 917 (39.4%) patients in the placebo group (HR=0.76, p<0.001). The rate of first hospitalization due to CV events was 29.3% in the dronedarone group vs. 36.9% in the placebo group (HR=0.74, p<0.001). This reduction in first CV hospitalization favoring dronedarone, was driven by a reduction in hospitalization due to AF (HR=0.63, p=<0.001) and ACS (HR=0.70, p=0.03). Death from any cause was not different between treatment groups (116 with dronedarone and 139 with placebo, p=0.18). However, death from CV causes was lower with dronedarone (63 events) vs. placebo (90 events; HR=0.71, p=0.03). The difference in number of deaths from cardiac arrhythmias was statistically different: 26 with dronedarone and 48 with placebo (p=0.01). The prevalence of abnormal liver function tests, endocrine events (hyper- and hypo-thyroidism), or interstitial lung disease were not different vs. placebo. Side effects more common with dronedarone were gastrointestinal (GI) disorders, mainly diarrhea and nausea, bradycardia, QT prolongation, rash, and increased serum creatinine. GI side effects (12.7%) were the main reason for discontinuation of therapy with dronedarone vs. placebo (8.1%). However, rate of discontinuation of ~30% due to any adverse event were similar in both treatment groups.

The authors concluded that dronedarone was associated with a significant reduction in the rate of hospitalization due to CV events or death compared with placebo, without a significant increase in thyroid or pulmonary toxicities. However a mean follow up of 21 months may not have been long enough to see side effects such as pulmonary fibrosis which usually appears after 2 years of therapy with amiodarone.

DIONYSOS

The finalized results of DIONYSOS are awaiting publication. Dronedarone was compared to amiodarone in 504 patients for a mean follow up of 7 months.[13] Preliminary data shows that the primary endpoint (recurrence of AF or discontinuation of the drug due to lack of efficacy or intolerance) was higher in the dronedarone group vs. the amiodarone group (73.9% vs. 55.3%, respectively). Patients in the dronedarone group had greater AF recurrence rates (36.5%) compared to patients in the amiodarone group (24.3%). Fewer patients discontinued dronedarone prematurely compared to amiodarone (26 patients vs. 34 patients, respectively). Patients on drone-

Table 3. Effects of other drugs on dronedarone.

DRUG	EFFECT	MECHANISM
• Azole antifungals (ketoconazole,itraconazole) • Nefazodone • Ritonavir • Erythromycin • Clarithromycin • Grapefruit juice	↑ dronedarone exposure (Ketoconazole ↑dronedarone exposure by 17-fold & Cmax by 9-fold)	Potent CYP3A4 inhibition
• Rifampin • Carbamazepine • Phenobarbital • Phenytoin • St. John Wort	↓ dronedarone exposure (Rifampin increases dronedarone exposure by 80%)	CYP3A4 induction
• Verapamil • Diltiazem	↑dronedarone exposure by 1.4-to 1.7-fold ↓HR	Moderate CYP3A4 inhibition and pharmacodynamic interaction
• Grapefruit juice	↑ dronedarone exposure 3-fold and Cmax 2.5-fold	CYP3A inhibition

Table 4. Effects of dronedarone on other drugs.[9]

DRUG	EFFECT	MECHANISM
Digoxin	↑ concentration 2.5-fold	P-glycoprotein
Simvastatin	level ↑ 4- & 2-fold, respectively	CYP3A4 inhibition
Metoprolol	level ↑ 1.6-fold	CYP2D6 inhibition
Propranolol	level ↑ 1.3-fold	CYP2D6 inhibition
β-blockers, TCAs, SSRIs	↑ plasma concentration	CYP2D6 inhibition
Verapamil, Diltiazem or Nifedipine	level ↑ 1.4-to 1.5-fold	CYP3A4
Cyclosporine, Sirolimus, Tacrolimus	↑ plasma concentration	CYP3A4 inhibition

SSRIs=selective serotonin reuptake inhibitors; TCA= tricyclic antidepressants.

darone had fewer thyroid and neurologic side effects. Dronedarone was correlated with fewer occurrences of bradycardia, and QT prolongation than amiodarone. GI side effects such as diarrhea, vomiting, and nausea, were more common with dronedarone.[12] The small sample size and limited duration of follow up make it difficult to statistically interpret the findings from this superiority trial.

SAFETY

Results from the ANDROMEDA trial led to a box warning from the FDA that discourages dronedarone use in patients with NYHA class IV HF and in NYHA class II/III HF with a recent decompensation that requires hospitalization. Patients need to be advised to contact their physician at any signs of weight gain, edema, or shortness of breath.[10]

The effect of dronedarone on renal function was assessed in 15 healthy individuals. Dronedarone reduced renal creatinine clearance by about 18% without reducing renal sinistrin clearance compared to placebo. This indicates no effect on glomerular filtration rate but a partial inhibition of tubular organic cation transporters that lead to a potential interaction with cationic drugs.[13] The increase in serum creatinine (SrCr) concentration happens quickly, reaches a plateau after 7 days and reverses after discontinuation. The plateau SrCr concentration should be used as the patient's new baseline.[10]

Dronedarone should not be given with drugs that are strong CYP3A inhibitors or those that have the potential to prolong the QT interval, such as class I and III antiarrhythmics (e.g. ibutilide, quinidine, procainamide, dofetilide, amiodarone), fluoroquinolones, or ritonavir to avoid the risk of developing Torsade de Pointes (Tables 3 & 4). Dronedarone is contraindicated in patients with second- or third-degree AV block, sick sinus syndrome (if not on pacemaker), bradycardia < 50 bpm, PR interval > 280 ms, and should be stopped if the QTc interval is ≥ 500 ms. The drug is classified in pregnancy category X and should be avoided in nursing women because its excretion in human milk is unknown. Safety and efficacy have not been studied in people under the age of 18 and in severe hepatic impairment.[10]

Dronedarone has the potential to cause hypokalemia and hypomagnesemia; therefore, monitoring is warranted when potassium- or magnesium-depleting diuretics are used concomitantly. Also use caution when coadministering with drugs that decrease AV node conduction such as beta-adrenergic antagonists and non-dihydropyridine calcium-channel blockers.[10]

The most common adverse events are diarrhea, nausea, vomiting, abdominal pain and asthenia (Table 5). Photosensitivity reactions have been reported in <1%.[10]

Table 5. Adverse effects of dronedarone in clinical trials.

ADVERSE EFFECT	DRONEDARONE	PLACEBO
Diarrhea	9%	6%
Nausea	5%	3%
Abdominal Pain	4%	3%
Vomiting	2%	1%
Dyspepsia	2%	1%
Asthenia	7%	5%
Bradycardia	3%	1%
Skin (rash, pruritus, eczema, dermatitis)	5%	3%
Serum creatinine increase ≥ 10% after 5 days of treatment	51%	21%
QTc prolongation (>450 ms in males >470 ms in females)	28%	19%

INDICATION, DOSAGE AND COST

The approved indication, based on the ATHENA study, is to reduce the risk of CV hospitalizations in patients with paroxysmal or persistent AF, with a recent episode of AF/AFL and CV risk factors (age > 70, hypertension, diabetes, prior cerebrovascular accident, LA diameter > 50 mm or LVEF < 40%) who are in sinus rhythm or will be cardioverted. [10] The recommended dose is 400 mg twice daily by the oral route. This dose should be administered with the morning and evening meals to increase bioavailability.[10] Dronedarone is available as 400 mg oral tablets and the average retail price of a 30-day supply is $274.32, ranging from $265.99 to $286.99.

SUMMARY

Dronedarone significantly decreases time to AF/AFL recurrence, CV hospitalizations, and death due to CV events compared to placebo. No reports of serious extra cardiac toxicities, such as thyroid and pulmonary diseases, have been noted with dronedarone in clinical trials. Emphasis should be placed on using dronedarone in the appropriate patient and avoiding its use in patients with NYHA Class IV HF as well as those with NYHA class III/IV HF with recent decompensation that required hospitalization.

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REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119(3):480-6.
2. Alan S. Go, MD. The Epidemiology of Atrial Fibrillation in Elderly Persons: The Tip of the Iceberg. Am J Geriatr Cardiol 2005;14(2):56-61.
3. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114(7):e257-354.
4. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation 2003;108(6):711-6.
5. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347(23):1825-33.
6. MICROMEDEX Health Care Series online. Accessed August 10, 2009.
7. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360(7):668-78 .
8. Hohnloser SH, Connolly SJ, Crijns HJ, et al. Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter. J Cardiovasc Electrophysiol 2008;19(1):69-73.
9. Hoy SM, Keam SJ. Dronedarone. Drugs. 2009;69 (12):1647-63.
10. Sanofi-Aventis. Multaq (dronedarone) package insert. Bridgewater, NJ; 2009.
11. Køber L, Torp-Pedersen C, McMurray JJV, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358(25):2678-87.
12. Singh BN, Connolly SJ, Crijns HGJM, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357:987–99.
13. Howard PA. Dronedarone: Emergence of a new therapeutic option for the treatment of atrial fibrillation. Hospital Pharmacy 2009:44(7):562-568.
14. Tschuppert Y, Buclin T, Rothuizen LE, et al. Effect of dronedarone on renal function in healthy subjects. Br J Clin Pharmacol 2007;64(6):785-91.

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