The Global Aware Group

Appropriate Care For Women With Androgen Excess

Best practice in the treatment of hyperandrogenic skin symptoms

Educational Slide Kit

Module 3

The AWARE group is a panel of independent physicians with an expert interest in androgen excess in women. Formation of the AWARE group and its ongoing work is supported and funded by Bayer AG.

October 2018

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Testing your knowledge

1. What do you think is the most important goal of treatment of hyperandrogenic skin symptoms?

   A. Improve clinical symptoms i.e. reduce hair growth or number and severity of acne lesions
   B. Restore menstrual function
   C. Minimize psychological and QoL impairment
   D. It depends on the individual patient's needs and goals of treatment

Testing your knowledge

2. What is the aim of pharmacological treatment for the skin symptoms of androgen excess?

   A. Reducing amount of androgens produced
   B. Controlling androgen effects at tissue level
   C. Reducing the level of free testosterone
   D. All of the above

Testing your knowledge

3. Which of the following statements is true about antiandrogenic potential of EE/progestogen combinations?

   A. EE/progestogen combinations have no antiandrogenic potential
   B. Different combinations of EE/progestogen have varied antiandrogenic potential
   C. All EE/progestogen combinations have the same antiandrogenic potential
   D. None of the above

Testing your knowledge

4. A patient with androgen excess should always be referred if you suspect an androgen-secreting tumour. What other circumstances might you refer a patient with androgen excess?

   A. Undiagnosed bleeding
   B. Severe psychological morbidity for example, severe anxiety and/or depression
   C. Scarring acne
   D. Fertility problems

Module content

- Aims of treatment for hyperandrogenic skin symptoms
- Treatment options
- Rationale for antiandrogen treatment
- Role of antiandrogens as combined hormone treatment
- The AWARE treatment proposal

Aims of treatment for androgen excess

Goals of treatment for androgen excess[1-4]

- In women with **clinical hyperandrogenism**:
  - Improve clinical symptoms i.e. reduce hair growth or number and severity of acne lesions
  - Restore menstrual function (if needed)
  - Minimize psychological and QoL impairment

- In women with **biochemical hyperandrogenism**:
  - Reduce the risk of long-term metabolic and reproductive complications

1. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592; 2.Goodman NF, et al. Endocrin Pract 2015;21(11):1291–1300; 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38; 4. Lizneva D, et al. Fertil Steril 2016;106(1):6–15

Treatment options for hyperandrogenic skin symptoms

Overview of treatment options

- **Lifestyle management**
  - Aimed at reducing the risk of long-term metabolic consequences[1,2]
- **Topical or cosmetic options**[1]
  - Targets hyperandrogenic skin symptoms such as hirsutism and acne
- **Pharmacological treatment**[1]
  - Aimed at reducing the level of circulating androgens and controlling their effect at tissue level

1. Goodman NF, et al. Endocrin Pract 2015;21(11):1291–1300; 2. Moran LJ, et al. Cochrane Database Syst Rev 2011;16(2):CD007506

Lifestyle management[1]

Lifestyle management should be a core part of treatment to improve metabolic and psychological consequences associated with this condition[1-3]

*Where necessary to reduce weight/BMI[1]

1. Teede HJ, et al. Med J Aust. 2011 Sep 19;195(6):S65-112; 2. Goodman NF, et al. Endocrin Pract 2015;21(11):1291–1300; 3. Moran LJ, et al. Cochrane Database Syst Rev 2011;16(2):CD007506

Topical or cosmetic treatments options[1,2]

Cosmetic options for treatment of hirsutism mainly involve hair removal

- ✓ Shaving, plucking, or waxing
- ✓ Use of depilatory creams or epilators
- ✓ Electrolysis or laser hair removal
- ✓ Eflornithine cream

Topical options for treatment of acne mainly involve use of:

- ✓ Topical retinoids, such as isoretinoin or adpalene
- ✓ Azaleic acid
- ✓ Benzoyl peroxide
- ✓ Topical antiobiotics such as tetracyclines

1. Goodman NF, et al. Endocrine Pract 2015;21(11):1291–1300; 2. Moran LJ, et al. Cochrane Database Syst Rev 2011;16(2):CD007506

Pharmacological treatment options

Treatment is aimed at reducing the level of circulating androgens and controlling their effect at tissue level[1]

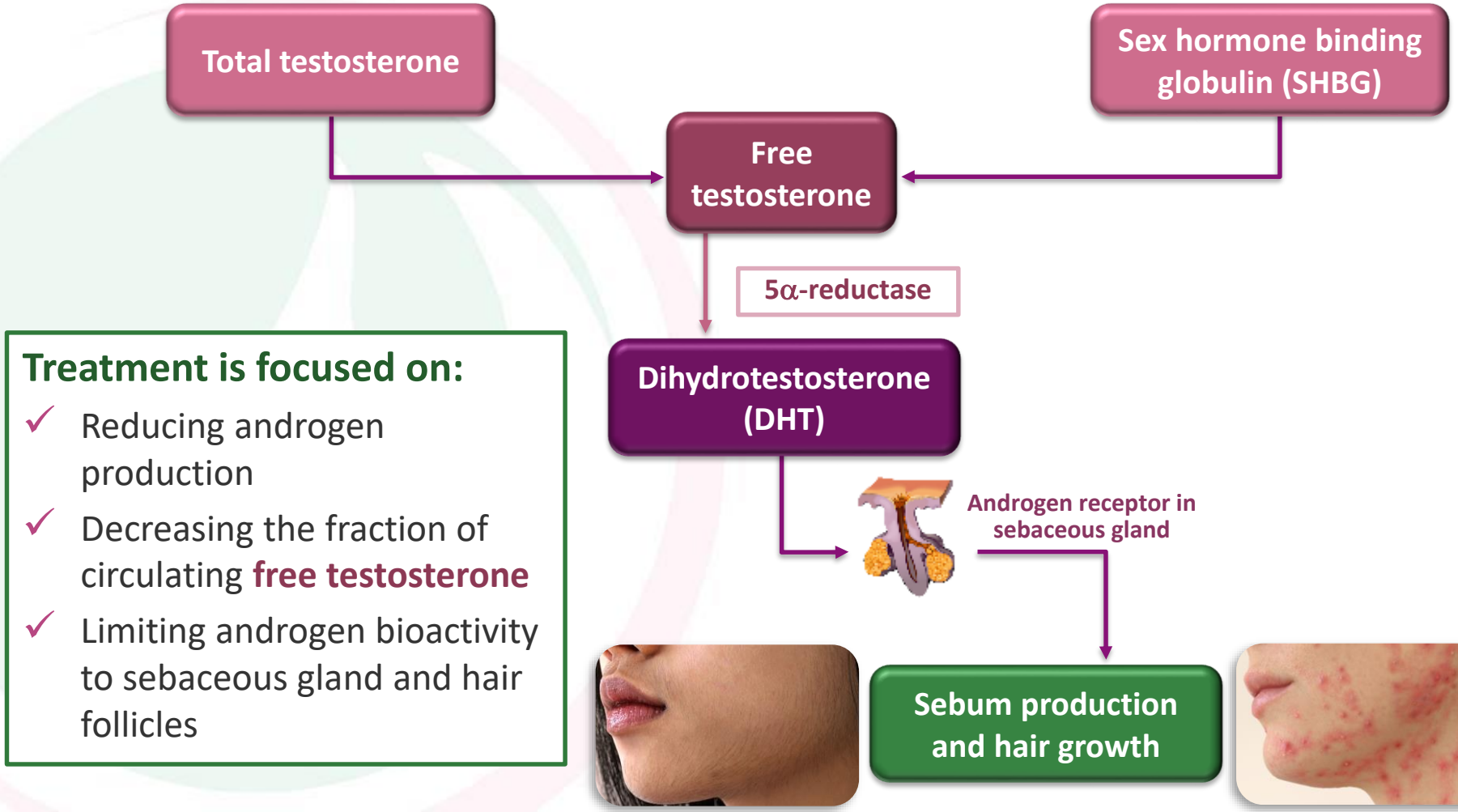
- ✓ Antiandrogens, such as cyproterone acetate and spironolactone
- ✓ Finasteride
- ✓ Insulin-sensitizers, such as metformin and pioglitazone
- ✓ GnRH* analogues, such as goserelin and leuprorelin

*Gonadotrophin-releasing hormone

1. Goodman NF, et al. Endocrin Pract 2015;21(11):1291–1300

Rationale for antiandrogen treatment

Antiandrogens in the treatment of skin symptoms such as hirsutism and acne[1-5]



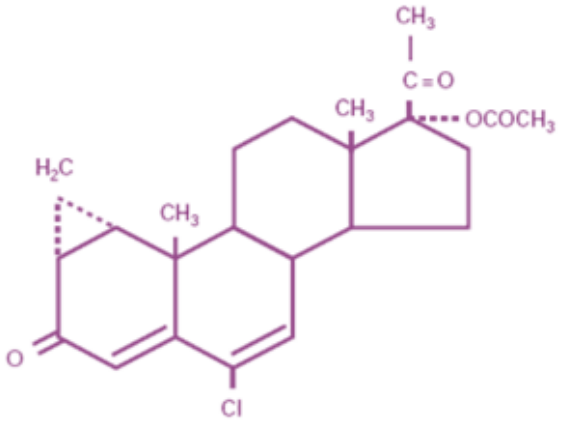
Treatment is focused on:

- ✓ Reducing androgen production
- ✓ Decreasing the fraction of circulating **free testosterone**
- ✓ Limiting androgen bioactivity to sebaceous gland and hair follicles

1. Goodman NF, et al. Endocrine Pract 2015;21(11):1291–1300; 2. Azziz R et al. Idiopathic hirsutism. Endocr Rev 2000; 21: 347–62; 3. Mofid A et al. Hirsutism. Int J Clin Pract 2008; 62: 433–43; 4. Neithardt AB, Barnes RB. Semin Reprod Med 2003; 21: 285–93; 5. Azziz R. Obstet Gynecol 2003; 101: 995–1007

Cyproterone Acetate (CPA): a steroidal antiandrogen[1-6]

CPA is a steroid compound with potent…



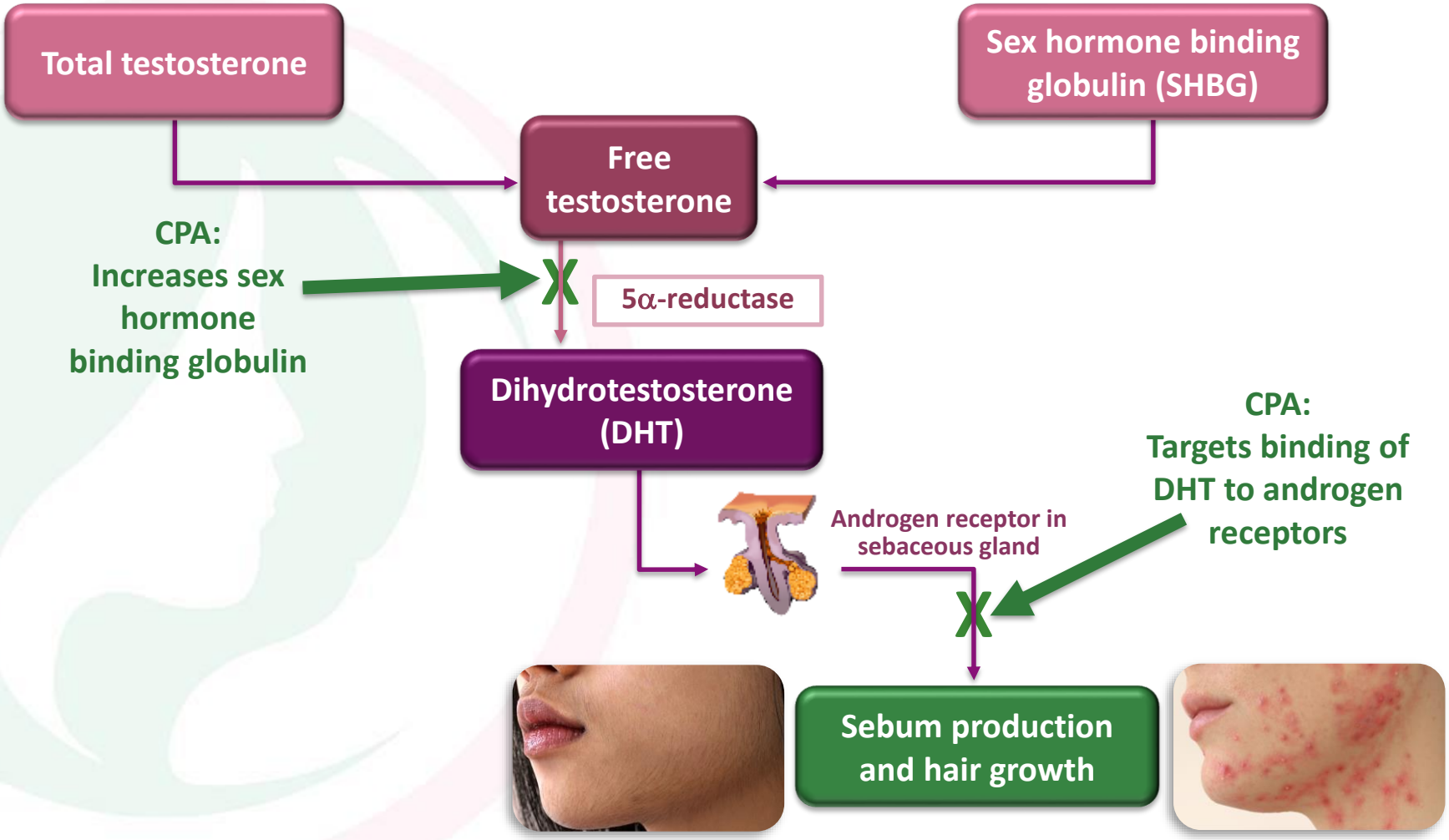
…Antigonadotropic properties

…Antiandrogenic activities

…Progestogenic activities

1. Neumann F. Exp Clin Endocrinol 1994;102:1–32; 2. Spona J & Huber J. Gynecol Obstet Invest 1987;23:184–93; 3. Fang S & Liao S. Mol Pharmacol 1969;5:428–31; 4. Fedele L, et al. Contraception 1987;35:497–505; 5. Neumann F. Postgrad Med J 1978;54 Suppl 2:11–24; 6. Aydinlik S, et al. Clinical Trials Journal 1990;27:392–402

CPA targets hyperandrogenic skin symptoms via two mechanisms

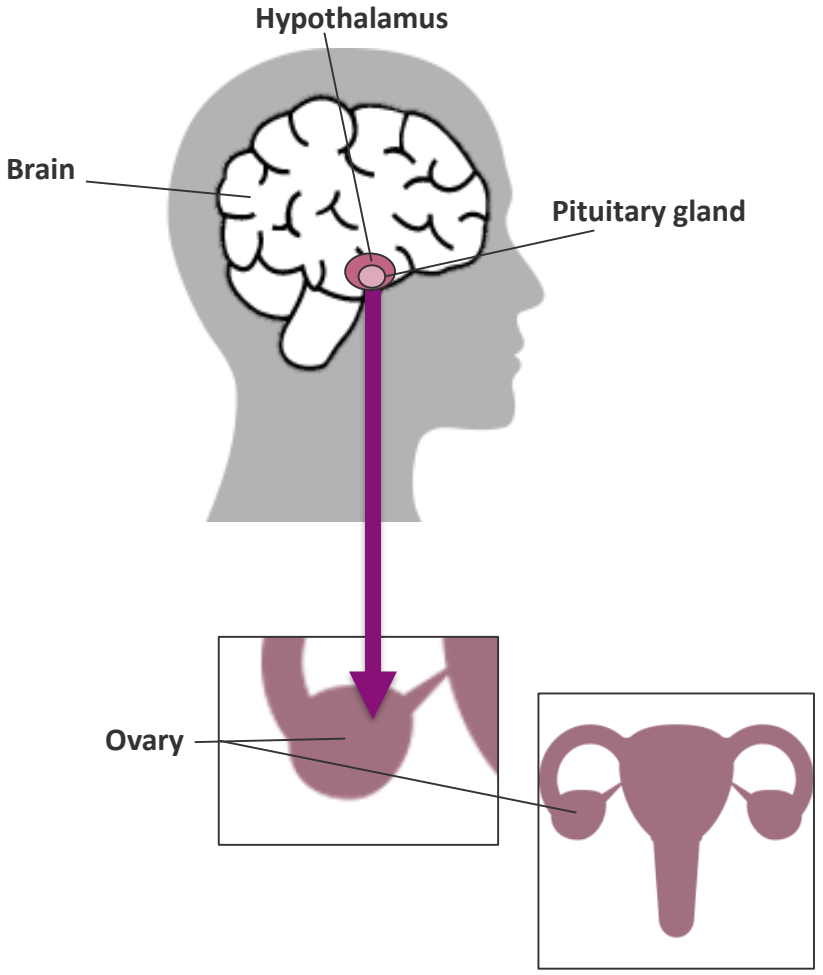


1. Neumann F. Exp Clin Endocrinol 1994;102:1–32; 2. Spona J & Huber J. Gynecol Obstet Invest 1987;23:184–93; 3. Fang S & Liao S. Mol Pharmacol 1969;5:428–31; 4. Fedele L, et al. Contraception 1987;35:497–505; 5. Neumann F. Postgrad Med J 1978;54 Suppl 2:11–24; 6. Aydinlik S, et al. Clinical Trials Journal 1990;27:392–402

CPA also affects synthesis and secretion of ovarian androgens[1-3]

CPA interacts with GnRH receptors in the pituitary gland blocking the release of LH and FSH

Inhibition of FSH and LH leads to a decline in ovarian androgen production and a reduction in free testosterone



CPA, cyproterone acetate; **FSH**, follicle stimulating hormone; **GnRH**, gonadotropin-releasing hormone; **LH**, luteinizing hormone

1. Badawy A & Elnashar A. Int J Womens Health. 2011;3:25-35; 2. Ruan X, et al. Eur J Contracept Reprod Health Care. 2017;22(3):183-190; 3. Barbieri RL. Trends Endocrinol Metab. 1992;3(1):30-4

Role of antiandrogens as combined hormone treatment

Different combinations of EE/progestogen have varied antiandrogenic potential[1-3]

Progestogen	CPA	CMA	DNG	DRSP
Mode of action	Inhibits the activity of 5-alpha-reductase and androgen synthesis in the skin and decreases androgen blood concentration through an antigonadotrophic effect.	Inhibits the activity of 5-alpha reductase in the skin and reduces ovarian and adrenal androgen production via its antigonadotrophic effect.	Possesses strong progestational effects and moderate Antiandrogenic and antigonadotrophic effects.	Blocks ovarian steroid production, reduces adrenal androgen synthesis and blocks peripheral androgen receptors in the skin.

- CPA/EE has the greatest antiandrogen potential of hormonal treatments containing a combination of progestogens and EE[4-5]

1. Sirmans SM, Pate KA. Clin Epidemiol 2014;6:1–13; 2. Zouboulis CC, et al. Horm Metab Res 2007;39:85–95; 3. Sitruk-Ware R. Hum Reprod Update 2006;12:169–178; 4. Bitzer J, et al. Eur J Contracept Reprod Health Care. 2017;22:172-182; 5. Ruan X, et al. Eur J Contracept Reprod Health Care. 2017;22(3):183-190

Combination CPA/EE* treatment effectively treats hyperandrogenic skin symptoms and menstrual dysfunction[1,2]

- Significant reduction in:[1]
  - Acne lesions count and severity at 6 months
  - Hirsutism score (mF-G) and use of cosmetic treatments at 6 months
  - Sebum production and seborrhea at 9 months
- Additional benefits of menstrual regularity and effective contraception[2]
- Reduction in long-term risk of endometrial hyperplasia and endometrial cancer[2]

***CPA/EE**, 0.035mg ethinylestradiol/2mg cyproterone acetate

1. Bitzer J, et al. Eur J Contracept Reprod Health Care. 2017;22:172-182; 2. Ruan X, et al. Eur J Contracept Reprod Health Care. 2017;22(3):183-190

Cardiovascular safety with EE/progestogen combinations

Use of estrogen/progestogen combinations is associated with an increased risk for VTE (DVT or PE)[1,2]

The use of CPA/EE carries an increased risk of VTE/ATE compared with no use or LNG/EE use

- Highest during the 1st year of use
- Highest when restarting or switching from another OC*

However, the risk of VTE during COC use remains **lower than that during pregnancy and childbirth**[3,4]

ATE, Arterial thromboembolism; **LNG**, levonorgestrel; **COC**, Combined oral contraceptive; **DVT**, Deep vein thrombosis; **PE**, Pulmonary embolism; **OC**, Oral contraceptive; **VTE**, Venous thromboembolism; **CPA/EE**, 0.035mg ethinylestradiol/2mg cyproterone acetate

1. OC class label; 2. Rosendaal MD. Lancet 1999;353(9157):1167–1173; 3. Dinger JC, et al. Contraception 2007;75(5):344–354; 4. Heit et al. Ann Intern Med 2005;143(10):697–706

Cardiovascular safety with EE/progestogen combinations (continued)

Due to its labeled indication, CPA/EE may channel use towards women with an inherently higher cardiovascular risk[1,2]

Observational studies of **VTE risk with CPA/EE** compared to LNG-containing and other COCs (low-estrogen <0.05mg) yield varying findings

Some studies reported a greater VTE risk, **comparable** to so-called 3rd generation COCs[3–5]

Other studies showed **no differences** in VTE risk[1,6,7]

Studies that addressed the issue of confounding or duration of use concluded that the VTE risk is **not significantly higher**[1,7]

COC, Combined oral contraceptive; **LNG**, Levonorgestrel; **PCOS**, Polycystic ovary syndrome; **VTE**, Venous thromboembolism; **CPA/EE**, 0.035mg ethinylestradiol/2mg cyproterone acetate.

1. Seaman HE, et al. Pharmacoepidemiol Drug Saf 2004;13(7):427–436; 2. Bird ST, et al. J Thromb Haemost 2013;11(6):1059–1068; 3. Vasilakis-Scaramozza C et al. Lancet 2001;358(9291):1427–9; 4. Seaman HE, et al. Hum Reprod 2003;18(3):522–6; 5. Lidegaard Ø, et al. Acta Obstet Gynecol Scand 2013;92(10):1135–1142; 6. Lidegaard Ø, et al. J Obstet Gynaecol Can 2003;25(7):575–7; 7. EURAS 2007

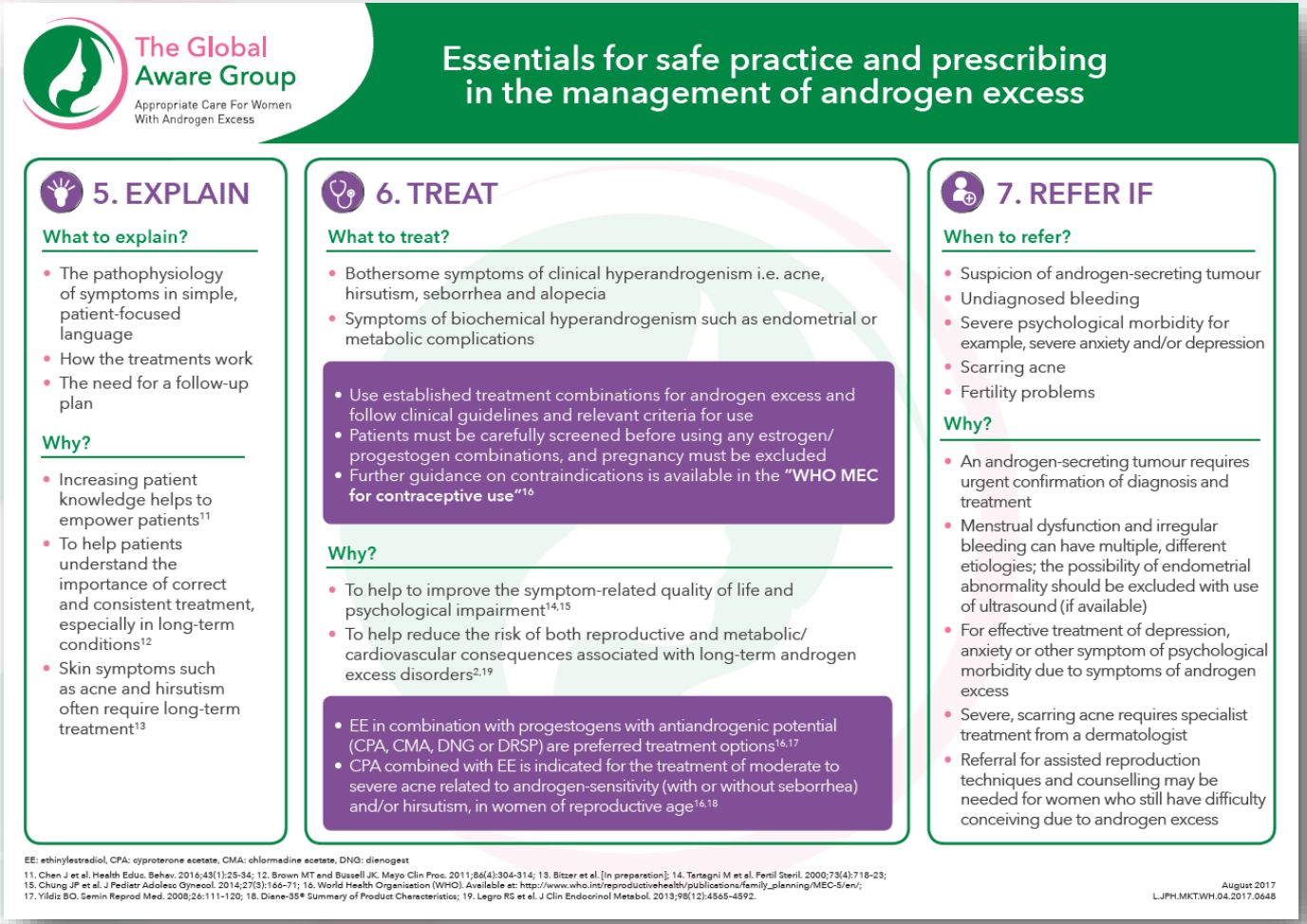
The AWARE treatment proposal

Challenges in the management of androgen excess[1]

- Identifying different presenting symptoms and their pathophysiology
- Understanding the role of non-hormonal and hormonal treatment
- Effective treatment of presenting clinical symptoms e.g. skin manifestations and menstrual dysfunction
- Identifying and managing associated syndromes e.g. polycystic ovary syndrome
- Managing patient expectations of treatment outcomes
- Balancing risks and benefits of long-term treatment through life stages
- Managing long-term metabolic syndrome and reproductive consequences

1. Redmond GP. Int J Fertil Womens Med 1998;43(2):91–7

The AWARE treatment proposal addresses these challenges



The Global Aware Group
Appropriate Care For Women With Androgen Excess

Essentials for safe practice and prescribing in the management of androgen excess

5. EXPLAIN

What to explain?

- The pathophysiology of symptoms in simple, patient-focused language
- How the treatments work
- The need for a follow-up plan

Why?

- Increasing patient knowledge helps to empower patients[11]
- To help patients understand the importance of correct and consistent treatment, especially in long-term conditions[12]
- Skin symptoms such as acne and hirsutism often require long-term treatment[13]

6. TREAT

What to treat?

- Bothersome symptoms of clinical hyperandrogenism i.e. acne, hirsutism, seborrhea and alopecia
- Symptoms of biochemical hyperandrogenism such as endometrial or metabolic complications

- Use established treatment combinations for androgen excess and follow clinical guidelines and relevant criteria for use
- Patients must be carefully screened before using any estrogen/progestogen combinations, and pregnancy must be excluded
- Further guidance on contraindications is available in the **"WHO MEC for contraceptive use"**[16]

Why?

- To help to improve the symptom-related quality of life and psychological impairment[14,15]
- To help reduce the risk of both reproductive and metabolic/cardiovascular consequences associated with long-term androgen excess disorders[2,19]

- EE in combination with progestogens with antiandrogenic potential (CPA, CMA, DNG or DRSP) are preferred treatment options[16,17]
- CPA combined with EE is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age[16,18]

7. REFER IF

When to refer?

- Suspicion of androgen-secreting tumour
- Undiagnosed bleeding
- Severe psychological morbidity for example, severe anxiety and/or depression
- Scarring acne
- Fertility problems

Why?

- An androgen-secreting tumour requires urgent confirmation of diagnosis and treatment
- Menstrual dysfunction and irregular bleeding can have multiple, different etiologies; the possibility of endometrial abnormality should be excluded with use of ultrasound (if available)
- For effective treatment of depression, anxiety or other symptom of psychological morbidity due to symptoms of androgen excess
- Severe, scarring acne requires specialist treatment from a dermatologist
- Referral for assisted reproduction techniques and counselling may be needed for women who still have difficulty conceiving due to androgen excess

EE: ethinylestradiol, CPA: cyproterone acetate, CMA: chlormadine acetate, DNG: dienogest

11. Chen J et al. Health Educ. Behav. 2016;43(1):25-34; 12. Brown MT and Bussell JK. Mayo Clin Proc. 2011;86(4):304-314; 13. Bitzer et al. [in preparation]; 14. Tertagni M et al. Fertil Steril. 2000;73(4):718-23; 15. Chung JP et al. J Pediatr Adolesc Gynecol. 2014;27(3):166-71; 16. World Health Organisation (WHO). Available at: http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/; 17. Yildiz BO. Semin Reprod Med. 2008;26:111-120; 18. Diane-35® Summary of Product Characteristics; 19. Legro RS et al. J Clin Endocrinol Metabol. 2013;98(12):4565-4592.

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Important elements of patient communication when discussing treatment[1-3]

5. EXPLAIN

What to explain?

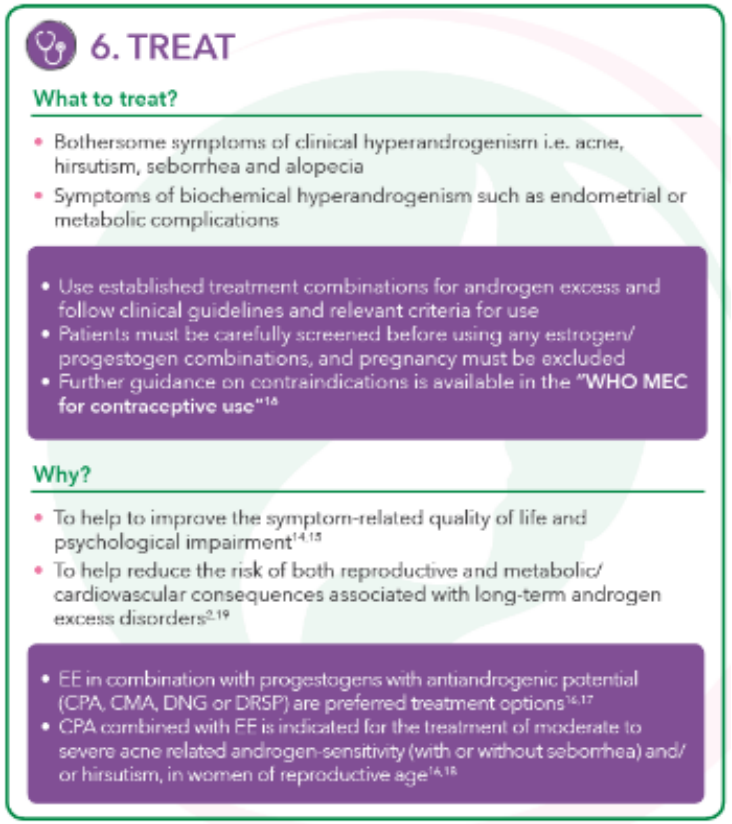
- The pathophysiology of symptoms in simple, patient-focused language
- How the treatments work
- The need for a follow-up plan

1. Chen J, et al. Health Educ Behav 2016;43(1):25-34; 2. Brown MT & Bussell JK. Mayo Clin Proc. 2011:86(4):304-314; 3. Bitzer J, et al. Eur J Contracept Reprod Health Care. 2017;22:172-182

Treatment needs to be targeted at all symptoms

- **Effective treatment** of seborrhea, acne, hirsutism and alopecia can help to **improve quality of life** and psychological impairment associated with clinical hyperandrogenism[1,2]

- Hyperandrogenic skin symptoms can arise due to **biochemical hyperandrogenism**, treatment of which can help reduce the risk of both reproductive and metabolic/ cardiovascular consequences associated with long-term androgen excess disorders[3,4]



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1. Tartagni M, et al. Fertil Steril. 2000;73(4):718–23; 2. Chung JP, Yiu AK, Chung TK, et al. J Pediatr Adolesc Gynecol. 2014;27(3):166–71; 3. Fauser BCJM, et al. Am Soc Rep Med. 2012;97(1):28-38.e25; 4. Legro RS, et al. J Clin Endocrinol Metabol. 2013;98(12):4565–4592

Factors to consider before prescribing combined hormonal treatment

- Use established treatment combinations for androgen excess

  - EE in combination with progestogens with antiandrogenic potential (CPA, CMA, DNG or DRSP) are preferred treatment options.[1,3]
  - CPA combined with EE, is indicated for the treatment of **moderate to severe acne** related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age.[1,2]

- Screen patients using WHO MEC for guidance in the prescribing of estrogen/progestogen combinations[1]

1. WHO MEC. 5th ed. 2015; 2. Yildiz BO. Semin Reprod Med. 2008;26:111–120; 3. Dianette SmPC

When to refer women with androgen excess[1,2]

7. REFER IF

When to refer?

- Suspicion of androgen-secreting tumour
- Undiagnosed bleeding
- Severe psychological morbidity for example, severe anxiety and/or depression
- Scarring acne
- Fertility problems

1. Fauser BCJM, et al. Am Soc Rep Med. 2012;97(1):28-38.e25; 2. Legro RS, et al. J Clin Endocrinol Metabol. 2013;98(12):4565–4592

Conclusions

- Treatment of androgen excess aims to:[1-5]
  - Reduce the level of circulating androgens and control their effect at tissue level
  - Improve clinical hyperandrogenic skin symptoms and associated psychological impairment[6] and restore menstrual regularity where needed
  - Reduce the risk of long-term reproductive and metabolic consequences of biochemical hyperandrogenism
- Options include cosmetic or topical treatments, pharmacological therapy and lifestyle management[1,7]
- CPA/EE offers effective treatment of hyperandrogenic skin symptoms and menstrual dysfunction[8]

1. Goodman NF, et al. Endocrine Pract 2015;21(11):1291–1300; 2. Azziz R et al. Idiopathic hirsutism. Endocr Rev 2000; 21: 347–62; 3. Mofid A et al. Hirsutism. Int J Clin Pract 2008; 62: 433–43; 4. Neithardt AB, Barnes RB. Semin Reprod Med 2003; 21: 285–93; 5.Azziz R. Obstet Gynecol 2003; 101: 995–1007; 6. Brady C, et al. Drug, Healthc and Patient Saf 2009:1 9-15; 7. Moran LJ, et al. Cochrane Database Syst Rev 2011;16(2):CD007506. doi: 10.1002/14651858.CD007506.pub2; 8. Ruan X, et al. Eur J Contracept Reprod Health Care. 2017;22(3):183-190

Testing your knowledge

1. What do you think is the most important goal of treatment of hyperandrogenic skin symptoms?

   A. Improve clinical symptoms i.e. reduce hair growth or number and severity of acne lesions
   B. Restore menstrual function
   C. Minimize psychological and QoL impairment
   D. It depends on the individual patient's needs and goals of treatment[1-4]

1. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592; 2.Goodman NF, et al. Endocrin Pract 2015;21(11):1291–1300; 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38; 4. Lizneva D, et al. Fertil Steril 2016;106(1):6–15

Testing your knowledge

2. What is the aim of pharmacological treatment for the skin symptoms of androgen excess?

A. Reducing amount of androgens produced
B. Controlling androgen effects at tissue level
C. Reducing the level of free testosterone
D. All of the above[1]

1. Goodman NF, et al. Endocrine Pract 2015;21(11):1291–1300

Testing your knowledge

3. Which of the following statements is true about antiandrogenic potential of EE/progestogen combinations?

A. EE/progestogen combinations have no antiandrogenic potential

B. Different combinations of EE/progestogen have varied antiandrogenic potential[1-3]

C. All EE/progestogen combinations have the same antiandrogenic potential

D. None of the above

1. Sirmans SM, Pate KA. Clin Epidemiol 2014;6:1–13; 2. Zouboulis CC, et al. Horm Metab Res 2007;39:85–95; 3. Sitruk-Ware R. Hum Reprod Update 2006;12:169–178

Testing your knowledge

4. A patient with androgen excess should always be referred if you suspect an androgen-secreting tumour. What other circumstances might you refer a patient with androgen excess?

A. Undiagnosed bleeding [1,2]
B. Severe psychological morbidity for example, severe anxiety and/or depression[1,2]
C. Scarring acne[1,2]
D. Fertility problems[1,2]

1. Fauser BCJM, et al. Am Soc Rep Med. 2012;97(1):28-38.e25; 2. Legro RS, et al. J Clin Endocrinol Metabol. 2013;98(12):4565–4592

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https://www.emas-online.org/nonemaseducationalmaterials/

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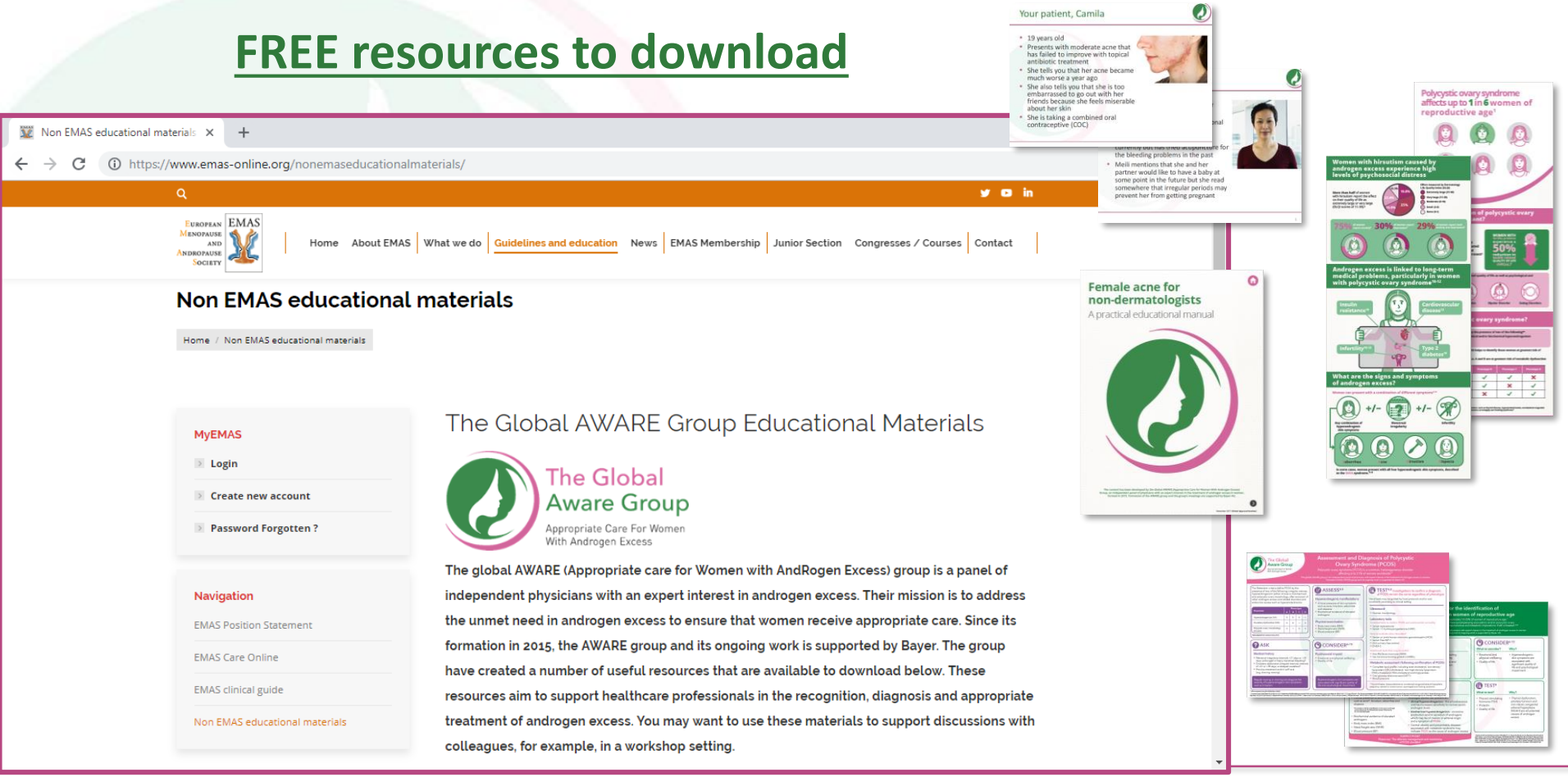

The AWARE group is a panel of independent physicians with an expert interest in androgen excess in women. Formation of the AWARE group and its ongoing work is supported and funded by Bayer AG.