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#### **Review Article**

# Adult-onset acne: An expert consensus

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#### ABSTRACT

Despite the increasing incidence of adult acne in recent times practical guidelines for management of these patients are lacking in India setup. Thus, to develop practical consensus-based recommendations on diagnosis and management of acne in adult patients an expert panel was finalized. The consensus was developed using Delphi method. Panel members were asked to complete two Delphi surveys one for diagnosis and another for management. Experts reached consensus on practical approach of diagnosis and management of patients with adult acne based on available evidence and their personal experience. Experts recommended that a holistic treatment approach consisting of standard therapy, adjuvant therapy and cosmetic use should be first choice treatment strategy in adult acne patients. Experts also commented that treatment choices should be individualized based on the specific characteristics of each patient and be tailored to suit this particular population.

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#### 1. Introduction

Acne is a pleomorphic disorder that can manifest at any time during life but is most commonly seen between the ages of 12 to 24, which estimates of 85% of population affected. It is among the most common dermatological conditions worldwide, with an estimated 650 million people affected. <sup>1,2</sup>

Despite being considered as a disease of adolescent age group, recently it has been observed that the incidence and prevalence of adult patients with acne is on the rise.<sup>3,4</sup> Various authors has reported that the incidence of acne in patients of age group between 26 – 44 years is increasing. Perkins et al in their study reported that the incidence of acne in adult females is in the range of 12%–22%.<sup>5</sup> Similarly Poli F et al concluded that in 41% patients acne persists in their adulthood.<sup>6</sup> In the same study authors reported that in 78% of the females there is worsening of

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acne during premenstrual period.<sup>6</sup> Goulden V et al in their study involving more than 700 people older than 25 years concluded that facial acne were reported by 12% of women and 3% of men.<sup>7</sup>

Despite this increase in incidence of adult acne, guidelines for management of these patients are lacking. Hence there are multiple apprehensions in the mind of dermatologist while managing such patients regarding which investigations to be done, which treatment regime is best suited for that patient, etc.

With this background, it was decided to develop consensus recommendations for diagnosis and management acne in adult patients in India.

#### 2. Materials and Methods

The consensus document was developed using a modified Delphi method by a panel of subject experts. A multidisciplinary panel of experts was selected according to their clinical experience, their interest in the field as

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reflected by their international publications, and further, on their experience in generating guidelines. In order to develop the clinical statements for the consensus process, an electronic search of the PubMed database was performed. A thorough literature search was conducted to identify relevant articles written in English using keywords for adult acne management that were paired with terms such as diagnosis, hirsutism, female acne, late onset acne, treatment, isotretinoin, hormonal therapy in acne, retinoids and hyperandrogenism. The final results of the literature searches were distributed among the panel members, including electronic full-text versions. Experts were asked to review the articles identified during the literature searches for evidence gaps and areas of ambiguity for managing adult acne to assist with the development of clinical statements. Panel members were asked to complete two Delphi surveys one for diagnosis and another for management. Each survey was followed by a meeting (face to face), during which results were presented and statements were discussed.

The statements were categorized as follows:

- 1. Consensus: Statements achieving a mean score of 7.00 or higher and having no more than one outlier.
- 2. Near consensus: Statements achieving a mean score of 6.50 or higher and having no more than two outliers.
- No consensus: Statements that did not meet the criteria of consensus or near consensus.

After each round, statements with a near or no consensus were discussed to determine whether they should be refined and added to the following Delphi survey or omitted completely. This methodology did not require the ethics committee approval.

#### 3. Results and Discussion

Following recommendations were made in the Delphi rounds.

#### 3.1. Laboratory Investigations

In the presence of other clinical signs of hyperandrogenism, all the panel members suggested plasma concentrations of free and total testosterone, S-DHEA, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and, in some cases, when suspecting PCOS, transvaginal ultrasound for visualization of the ovaries. These investigations should always be performed in the follicular phase, preferably between the first and fifth day of the menstrual cycle and the collection should be done in the morning, between 8 and 10 am. In this way, the hormonal variations of the menstrual cycle interfere less with blood analysis.

In suspected PCOS, the following criteria should be checked: presence of menstrual alterations (amenorrhea or oligomenorrhea), clinical and/or biochemical and/or hyperandrogenism, as well as ultrasonographic changes

(presence of 12 or more follicles with 2 and 9 mm of diameter or increase in ovarian volume > 10cm<sup>3</sup>). Figure 1 presents a scheme for laboratory investigation of adult acne. Although most adult acne patients show no signs of clinical or laboratory hyperandrogenism, slightly elevated levels of S-DHEA have been observed. DHT could be useful as a primary marker of peripheral androgen production. A distal metabolite of DHT, produced in androgen-responsive tissues, is 3-alpha, 17-beta-androstanediol glucuronate. This metabolite can be used as a marker of hyperandrogenism, especially in women with idiopathic hirsutism.

#### 4. Treatment

Adult acne is a therapeutic challenge because it presents a tendency to relapse, even after cycles of oral antibiotics or isotretinoin. The typical evolution of adult acne, with frequent relapses, makes maintenance treatment essential. According to panel members numerous factors should be considered while managing a patient of adult acne such as its severity, response to previous treatments, psychosocial impact, possibility of pregnancy, slow response to treatment and increased risk of sensitive skin irritation. Individual preferences and costs should also be considered.

According to experts' topical therapies are recommended in management of mild to moderate grades of acne and during maintenance therapy. Topical retinoids or combination of topical retinoids plus benzoyl peroxide (BPO) is recommended in both males and non-pregnant female patients with mild grade of adult acne. Experts recommended use of topical or systemic antibiotics and/or hormonal therapies along with topical retinoids and BPO in patients with moderate grades of adult acne. Patients with severe grade of acne should be treated with oral isotretinoin. In patients not responding to oral isotretinoin systemic antibiotics and/or hormonal therapies are recommended.

In pregnant, lactating females or females who are planning pregnancy topical azelaic acid 20% is recommended.

## 4.1. Retinoids

Adapalene and tretinoin are most commonly used topical retinoids in India. Both the drugs have proven efficacy and safety in management of acne.

# 4.2. Adapalene

Multiple clinical studies have established the efficacy and safety of adapalene in patients with adult acne. Berson D et al in their study in patients with adult acne reported that adapalene was associated with significant improvement in both inflammatory lesions (-61%) and non-inflammatory lesions (-51%) after 12 weeks of treatment with adapalene compared to vehicles (P = 0.045). Thielitz A et al. reported similar results with 0.1% adapalene with good tolerance. <sup>10</sup>

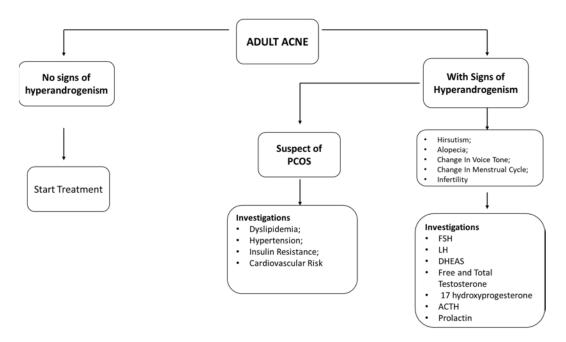
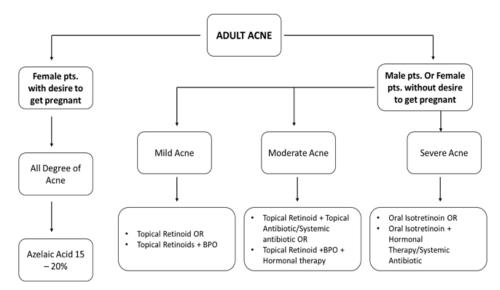


Fig. 1: Laboratory investigations of Adult Acne



GENERAL CARE AND GUIDELINES: Cleansing agents, Moisturizers, Sunscreens, Diet, Lifestyle

Associated Procedures: Extraction of Comedones, Drainage of Cysts, Lasers, Peelings and Light Therapies

Corticosteroids can be used in patients with congenital adrenal hyperplasia

Fig. 2: Represents the management algorithm for adult acne.

Considering the relative better safety profile of adapalene especially adapalene with microsphere technology, experts commented that adapalene should be considered in all patients with mild acne and as maintenance therapy.

#### 4.3. Tretinoin

According to experts, tretinoin is good alternative to adapalene in patients with adult acne. Berger R et al. in their study reported that microsphere tretinoin in concentration range of 0.04% to 0.1% is associated with significant improvement in inflammatory acne in adolescents and adults. <sup>11</sup>

## 4.4. Topical Antibiotics

Antibiotics plays very important role in management of acne. Because of their direct anti-inflammatory activity and inhibitory action of P. acnes topical antibiotics have very good efficacy in patients with acne. However, considering the increase in prevalence of resistance to antibiotic <sup>12</sup> experts recommended that topical antibiotic should never be used as monotherapy.

#### 4.5. Benzoyl peroxide (BPO)

According to experts because of its multimodal mechanism of action and synergistic activity with other topical antiacne medications BPO in combination with retinoids or topical antibiotics is useful in management of patients with mild to moderate grades of adult acne. According to experts BPO above 5% are not recommended for use in adults especially in females because of increased risk of contact irritant dermatitis. <sup>12</sup>

#### 4.6. Retinoids + Benzoyl peroxide

Combination of topical retinoids with BPO have synergistic activity which is associated with rapid onset of action and significant reduction in lesion within first week. <sup>13</sup>Gold LS et al in their meta-analysis concluded that combination therapy with adapalene 0.1% and 2.5% benzoyl peroxide gel is associated with significant improvement in acne lesions compared to the vehicle in women 25 years of age or older. <sup>13</sup> Considering these facts, experts recommended that the combination should be considered as first line therapy in management of adult patients with mild acne.

#### 4.7. Antibiotics + Benzoyl peroxide

According to experts BPO reduces the development of antibiotic resistance, hence combination of BPO along with topical antibiotics can be considered in patients with adult acne especially with pustular acne. Kircik LH et al in their study in 20 patients with adult acne reported that the combination of BPO and clindamycin is associated

with 70% and 58% decrease in inflammatory and non-inflammatory lesion after 12 weeks of therapy. On further continuation of therapy for 24 weeks the improvement was 93% and 90%, respectively. There were no serious adverse events. Based on these results authors concluded that the combination of clindamycin and BPO can be used as initial as well as maintenance therapy in management of acne. <sup>14</sup>Experts were also of same opinion.

#### 4.8. Azelaic acid

According to experts, comparable efficacy, favourable tolerability profile and high rates of satisfaction compared to other topical therapies in patients with mild to moderate acne makes azelaic acid promising alternative in management of patients with adult acne. Various clinical studies have established the efficacy and safety of azelaic acid in management of adult acne. Kainz JT et al concluded that topical azelaic 20% treatment significantly improved the quality of life of patients and reduced the severity of acne in adult patients. 15 In a study by Kircik LH et al, azelaic acid 15% gel, was associated with significant reduction in acne and post-inflammatory pigmentation. 16 Rocha MAD et al reported similar results in their study with azelaic acid 15%. 17 Azelaic acid is pregnancy category B drug, hence according to experts azelaic acid can be considered as first line therapy in pregnant and breastfeeding females.

## 5. Systemic Antibiotics

Systemic antibiotics are first choice drugs in management of patients with moderate to severe acne. The combination of systemic antibiotics with topical antiacne medications have synergistic activity, faster onset of action and shorter duration of therapy. <sup>18</sup> Tetracycline and its derivatives are the first choice of antibiotics for the treatment of adult acne.

However, considering the scenario of antibiotic resistance in India, experts commented that, systemic antibiotics should not be used as monotherapy in the treatment of acne. <sup>18–20</sup> As mentioned earlier, BPO in the concentration of 2.5 to 5% should be considered in combination with systemic antibiotics because of synergistic action, faster response and avoidance of development of resistance. <sup>21</sup> Azelaic acid as well as topical retinoids are alternatives. <sup>22</sup>

# 6. Hormonal Therapies

Hormonal therapies are one of the most important treatment modalities in management of patients with adult acne especially in female patients. Because of their slow onset of action, hormonal therapies should always be used in combination with other antiacne therapies. Hormonal therapies are recommended even in patients with normal hormonal profile. Since hormonal agents are not associated with bacterial resistance and comparable safety profile, they represent very promising alternative to systemic antibiotics for long term therapy. <sup>18,22,23</sup>

According to experts, hormonal agents should be considered when patients is having severe seborrhoea, premenstrual worsening of symptoms, recalcitrant inflammatory acne despite repeated cycles of isotretinoin and in situations where contraception is required.

## 6.1. Androgen receptor blockers

Androgen receptor have been commonly used in management of patients with adult female acne. Commonly used agents are cyproterone acetate, spironolactone, drospirenone and flutamide. <sup>22,23</sup>

- 1. Cyproterone Acetate: It acts by blocking androgen receptors. It is often used in combination with estrogens in the OCP, with ethinyl estradiol (EE) 35 ug. When used as monotherapy, it is given from day 1 to 10 of the menstrual cycle. Menstrual abnormalities, breast tenderness, nausea, vomiting, fluid retention, leg edema and headache common adverse events. <sup>24,25</sup>
- 2. Spironolactone: According to experts, spironolactone is specifically useful in patients with polycystic ovarian disease. Sato et al in their study demonstrated that spironolactone 200mg/day was associated with significant improvement in acne in females and it is good option for severe, recurring, and widespread acne. <sup>26</sup> Plovanich M et al in their retrospective study found that there spironolactone is associated with good safety profile and potassium monitoring is not required in healthy females with acne. <sup>27</sup> Lessner E et al demonstrated that the combination therapy with spironolactone and topical retinoids provide a superior response compared to topical retinoids alone in adult females with acne. <sup>28</sup>

#### 6.2. Oral Contraceptive Pills

As per American Academy of Dermatologists and Global acne alliance, oral contraceptives (OCs) consisting of both estrogen and progestin should be considered as first choice therapies in management of female patients with acne. These agents are as effective as oral antibiotics in reducing acne lesions at 6 months of treatment. <sup>18,29–31</sup>

According to experts, while prescribing OCs, proper counselling of patients regarding risks and benefits to oral contraceptive therapies should be done.

#### 6.3. Common combinations used:

- 1. CPA 2 mg + EE 0.035 mg
- 2. Drospirenone 3 mg + Ethinyl estradiol 0.03 mg
- 3. Desogestrel 0.15 mg + Ethinyl Estradiol 0.03 mg
- 4. Desogestrel 0.15 mg + Ethinyl Estradiol 0.02 mg

Started on day 1 of menstrual cycle (if contraception is required) or day 5 (if date of menstruation is to be maintained). <sup>23</sup>

Insulin-sensitizing agents Metformin and thiazolidinediones (rosiglitazone/pioglitazone).

These agents act by improving insulin sensitivity, and subsequently, decrease circulating androgen levels. In addition, these agents have a role in the treatment of PCOD. Metformin is given in a dose of 500 mg- 2000mg/day. Its side effects are diarrhea, nausea, taste changes, and lactic acidosis. <sup>23</sup>

#### 6.4. Isotretinoin

Isotretinoin is associated with unique and multimodal mechanism of action which includes reduction in size and activity of sebaceous glands, anti-inflammatory activity because of modulation of TLR 2 expression and gene transcription mediated by Fox O. <sup>32,33</sup>Hence oral isotretinoin is recommended as first line therapy in patients with severe acne and in patients with no response to other antiacne therapies. <sup>18</sup> Because of increased risk of teratogenicity, isotretinoin should be used very cautiously in females of reproductive age group. According to experts, proper counselling of patients regarding teratogenicity and requirement of highly effective contraceptive method is very important.

The recommended daily dose is 0.5 to 1.0mg / kg, after meals, for a period of 6 to 12 months. <sup>34</sup> Multiple studies have evaluated the low dose regimes of isotretinoin in adult patients with acne. Boyraz N et al have demonstrated that both intermittent and continuous low-dose isotretinoin regimens are very well tolerated and effective as classical regimens in the treatment of moderate acne vulgaris. <sup>35</sup> Rademaker M et al evaluated the significant improvement in low grade adult acne with 5mg/day dose of isotretinoin. <sup>36</sup> Dhaked DR et al in their study concluded that isotretinoin 20mg given either daily or on alternate day was equally effective in adult patients with moderate to severe acne. <sup>37</sup>

According to experts, low dose isotretinoin regimens may be a useful option for adult acne resistant to topical and hormonal treatments because of reduced risk of adverse events. However, there is increased risk of relapse with low dose regimes of isotretinoin especially in patients with severe acne.

#### 6.5. Adjuvant treatments

#### 6.5.1. Cosmetic use

According to experts, cleansers and moisturizers are very important component of any therapeutic regimen for patient with adult acne especially in females. Use of cleansers and moisturizers is associated with improved patient adherence to therapy thus increasing the treatment outcomes. Experts commented that aqueous non-comedogenic moisturisers

containing minimal allergenic ingredients should be preferred.

Experts advised that sunscreens are very important adjuvants in patients with acne and should be recommended in all patients especially in patient who are increased risk of developing post inflammatory hyperpigmentation. According to experts, all skin care products and cosmetics should be anti-comedonal and oil free. <sup>38,39</sup>

#### 6.5.2. Niacinamide

Niacinamide is useful adjuvant in management of acne because of its multiple effects like antimicrobial activity, sebostatic property and anti-inflammatory effects. It is also useful in management of post inflammatory hyperpigmentation since it inhibits melanosome transfer. <sup>40</sup>

#### *6.5.3. Light therapy*

Lasers, blue light and blue– red light, intensed pulsed light, pulsed dye lasers and photodynamic therapy (PDT), used with or without photosensitising agents are useful in some patients with adult acne. <sup>41,42</sup> As per available evidence, light therapy should be best used as an adjuvant therapy along with standard therapy in management of patients with adult acne. <sup>18</sup> Because of their shorter duration patients may show better adherence to light therapies, however their long term safety and efficacy is not established. <sup>42,43</sup> Amongst the light therapies PDT provides the most consistent outcomes on inflammatory acne. <sup>42,44</sup> Ablative and non-ablative laser therapy can also be used to treat acne scarring. <sup>45</sup>

### 6.5.4. Chemical peels

According to experts, chemical peels can be sued as an adjunctive therapy or as maintenance therapy in patients with adult acne. Some of the common chemical peels which are recommended in patients with adult acne are, glycolic acid (30, 35, 50 or 70%), salicylic acid (20–30%) and Jessner's solution. 46,47

## 6.5.5. Mechanical procedures

Similar to other adjuvant modalities experts recommended that mechanical procedures such as comedone extraction, cautery, dermabrasion, etc can be useful in certain patients with adult acne. Comedone extraction at the time of ovulation may be associated with reduction in inflammatory lesions. <sup>48</sup> Dermabrasion is effective in patients with atrophic acne scars <sup>49</sup> and can also be combined with chemical peels. <sup>50</sup>

#### 6.5.6. Maintenance therapy

Acne is associated with increased likelihood of relapse even after prolonged treatment, hence according to experts, maintenance therapy is very important in patients with adult acne. As per experts recommends topical retinoids such as adapalene or tretinoin should be considered as first choice drugs as maintenance therapy. In females of reproductive age group azelaic acid 15 or 20% is good alternative. Experts commented that topical or systemic antibiotics should never be used as maintenance therapy.

# 6.6. Recommendations for therapy in special patient populations

#### 6.6.1. Patients who wish to become pregnant

Because of their relative safety during pregnancy, experts recommended that topical azelaic acid (15 or 20%) or BPO (2.5–5%) monotherapy should be considered as first choice therapy in such patients is recommended. Combination of BPO along with other antibiotic such as erythromycin or clindamycin can also be considered in patients with severe inflammatory acne. In patients who are not responding to topical antibiotics systemic erythromycin or clindamycin can be considered based on risk benefit ratio. In patients with nodulocystic acne, topical corticosteroids or a short course of systemic corticosteroids can be considered. Light treatment and superficial chemical peels are recommended as adjunctive therapy.

#### 6.6.2. Patients who are pregnant or breastfeeding

Azelaic acid is pregnancy category B drug. Even though there are no adequate and well-controlled studies in pregnant women for azelaic acid no harmful teratogenic effects were reported with topical azelaic acid (15 – 20%). <sup>18,22</sup> Considering these facts, experts commented that in pregnant and breast-feeding females azelaic acid should be considered as first choice drug.

In pregnant females with acne who are not responding to topical therapies systemic glucocorticoids or antibiotics (erythromycin or clindamycin) can be considered after the first trimester of pregnancy. Light treatment, mechanical procedures and chemical peels are recommended as adjunctive therapy, and skin care products and cosmetics may also be used.

## 7. Conclusion

Incidence of adult acne is on the rise and it have significant negative impact on quality of life of patients. Patients with adult acne requires different treatment approach compared to adolescent acne. A holistic treatment regimen which combines standard therapy along with adjuvant therapies are recommended in adult patients. In patients with adult acne, it is very important to individualized the treatment considering the specific characteristics and need of the patients. Patient education on factors including correct application of topical therapy, potential side-effects, likely time to clinical improvement and expected outcomes is important in encouraging adherence with therapy.

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#### 9. Disclaimer

This consensus reflects the best available evidence at the time of preparation. Adherence to this consensus may not ensure successful treatment in every situation. The treating physician must make the ultimate judgment regarding the choice of any specific therapy in the context of circumstances for individual case scenarios.

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#### 11. Conflicts of Interest

There are no conflicts of interest.

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