2015

The cause and treatment of acne vulgaris: fact versus fiction

https://hdl.handle.net/2144/13948

Boston University
THE CAUSE AND TREATMENT OF ACNE VULGARIS: FACT VERSUS FICTION

by

STEVEN WAN

B.S.E., Duke University, 2014

Submitted in partial fulfillment of the requirements for the degree of Master of Science

2015
Approved by

First Reader

Hee-Young Park, Ph.D.
Assistant Dean

Second Reader

Gwynneth Offner, Ph.D.
Director M.S. Medical Sciences Program
Associate Professor of Medicine
DEDICATION

I would like to dedicate this work to my grandfather. He always cared about my acne problem and never failed to pass on any advice that he could find.
ACKNOWLEDGMENTS

I would like to thank Dr. Offner for her dedication to the BU MAMS program which made all of this possible. I would also like to thank Dr. Park, my advisor, whose guidance and reassurances helped me through the semesters.
Acne vulgaris is a complicated disease. It is primarily caused by dead skin, excessive sebum, and bacteria proliferation, all of which clogs hair follicles. The nature of this disease can start as comedone acne that affects young children, which progress into inflammatory acne in adolescent. The disease can persist into adulthood and is even reported to affect those 40 years of age. In adulthood, acne is more prevalent in women than in men. In addition to scarring and other physical damage, acne can also be psychologically damaging, especially in adolescents and adults. This paper will attempt to elucidate the causes of acne which includes: hormone, diet, smoking, environment, and human biology. Then this paper will explain common treatments that include: oral antibiotics, isotretinoin, topical treatment, hormone therapy, and light and laser therapy. After establishing researched causes and treatments, this paper will look into misconceptions regarding acne. Since there are many myths surrounding acne, this paper will only visit a few well documented misconceptions. Finally, this paper will formulate some new areas of research that acne literature is lacking. Acne is a serious disease and new information and research must be done in order to clear up misconceptions and allow physicians to provide better treatment.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iv</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>v</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>vi</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xi</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Economical Cost</td>
<td>1</td>
</tr>
<tr>
<td>Social Cost</td>
<td>3</td>
</tr>
<tr>
<td>Specific aim and objective</td>
<td>4</td>
</tr>
<tr>
<td>CAUSES AND RISK FACTORS</td>
<td>5</td>
</tr>
<tr>
<td>Hormones</td>
<td>5</td>
</tr>
<tr>
<td>Diet</td>
<td>7</td>
</tr>
<tr>
<td>Smoking</td>
<td>8</td>
</tr>
</tbody>
</table>
Environment ........................................................................................................... 8

Biology .................................................................................................................. 9

TREATMENT .......................................................................................................... 10

Oral Antibiotics ..................................................................................................... 10

Tetracycline ............................................................................................................. 12

Doxycycline ............................................................................................................ 12

Minocycline ............................................................................................................. 13

Macrolides .............................................................................................................. 13

Trimethoprim +/- Sulfamethoxazole .................................................................... 14

Flouroquinolone ..................................................................................................... 15

Isotretinoin ............................................................................................................ 15

Topical Treatment .................................................................................................. 16

Retinoids ............................................................................................................... 16

Topical antibiotics ................................................................................................. 17

BPO ........................................................................................................................ 17

Fixed Dose ............................................................................................................. 18

Hormone Treatment ............................................................................................... 19

Androgen Receptor Blocker .................................................................................. 20

Adrenal Androgen Production Blocker ................................................................. 21

Ovarian Androgen Blocker ..................................................................................... 21

Laser and Light Based Treatment ......................................................................... 21

UVA/UVB ............................................................................................................... 23

viii
Blue + Red Light ................................................................. 23
PDT with ALA ........................................................................ 23
Infrared lasers ..................................................................... 24
Radiofrequency ................................................................. 24
PDL ..................................................................................... 25
KTP laser ............................................................................ 25
IPL ..................................................................................... 26
MISCONCEPTIONS .................................................................. 27
Diet ..................................................................................... 28
Hygiene ............................................................................... 28
Disease Course .................................................................... 28
FUTURE RESEARCH .............................................................. 30
Treatment ........................................................................... 30
Stress ................................................................................ 30
Culture ............................................................................... 31
Diet ..................................................................................... 31
CONCLUSION ........................................................................ 32
REFERENCES .......................................................................... 33
CURRICULUM VITAE ............................................................ 37
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sale of acne treatments in the US from 2011 to 2012</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Statistical comparisons of SCL 90-R and EPQ score between adults with acne and adults without acne.</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Regression models for acne prevalence and cigarette consumption</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>List of common oral antibiotics</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>Pathogenic targets of topical treatment</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>List of light and laser treatments and their targets</td>
<td>22</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Number of comedones and inflammatory facial acne during maturation of adolescent boys</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Comparison of adherence and effectiveness between fixed does and separate dose</td>
<td>19</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

ALA .......................................................... Aminolevulinic acid
BPO .......................................................... Benzoyl peroxide
DHEAS ....................................................... Dehydroepiandrosterone sulfate
E₂ ............................................................. Estradiol
EPQ .......................................................... Eysenck Personality Questionnaire
FSH .......................................................... Follicle stimulating hormone
GH .......................................................... Growth hormone
IGF-1 .......................................................... Insulin-like growth factor-1
IPL ............................................................ Intense pulse light
KTP .......................................................... Potassium titanyl phosphate
LH .......................................................... Luteinizing hormone
OC .......................................................... Oral Contraceptives
OTC .......................................................... Over the Counter
P. acnes ..................................................... Propionibacterium acnes
PDL .......................................................... Pulse dye laser
PDT .......................................................... Photodynamic therapy
SCL 90-R .................................................... Symptom checklist 90-revised
TEBG ........................................................ Testosterone-estrogen binding globulin
UVA .......................................................... Ultraviolet A
UVB .......................................................... Ultraviolet B
**INTRODUCTION**

Adult acne, or acne vulgaris, is a condition of skin inflammation. In teenagers, about 15 to 20 percent of the population will experience acne with more frequency among male than female (Acne: overview, 2013). However, after reaching adulthood, age 20 or up, it has been found that 73.3% of the population has experienced acne at some point with females being affected more (Collier et al., 2008). Symptoms of acne are divided into 3 categories: mild (clogged pores in the skin), moderate (appearance of pimples), and severe (higher counts of pimples and appearance of reddish and painful nodules) (Acne: overview, 2013). Acne is caused by hormonal stimulation of sebaceous glands and current studies have also shown a complex, underlying inflammation pathway (Eichenfield et al., 2015). Though many hypotheses have been raised about environmental causes of acne, one purported cause of concern is an individual’s diet. Though the mechanism behind it remains unclear, there is no clear association between a low carbohydrate diet and acne improvement (Mahmood, S. N., & Bowe, W. P., 2014). Current treatment favors over the counter (OTC) medication, specifically those with topical application (For Treating Acne, 2014). Hormonal treatments are also available as a secondary or complementary option to normal medication (Bettoli et al., 2015).

**Economical Cost**

The acne treatment market is unique in the pharmacology landscape in that it is a relatively cheap market. It is also an extremely stable market with predictable growth. As
the numbers in Table 1 indicate, there was a 3% annual growth from 2011 to 2012 in the acne treatment market. The stability and growth is due to the continuous presence of adolescents. The need for acne treatment will never decrease and will only see growth as the adolescent population becomes larger and larger (Big Suppliers, 2012). Further contributing to this growth is the increasing numbers of adults who will develop acne and seek treatment (Collier et al., 2008). Also, sales figures seen below in Table 1 only represent the OTC medication and do not account for prescription medication or hormonal treatment, which will inflate the total amount spent on acne treatment.

Table 1. Sales of acne treatments in the US from 2011 to 2012. An increasing amount of money is devoted to acne treatment each year. Adapted from ‘Big Suppliers Exhibit Abliilty To Move Market’, 2012.
Social Cost

In addition to the economic cost that acne imposes on society, there is also the social cost, which is harder to quantify. In addition to anxiety and depression, it has been found that adults with acne also have a higher tendency of experiencing suicidal thoughts (Gül, A. İ., & Çölgeçen, E., 2015). The results from the Symptom checklist 90-revised (SCL 90-R), which measures an individual’s self-reported psychiatric symptoms and negative stress level, and the Eysneck Personality Questionnaire (EPQ), which measures an individual’s self-reported neuroticism, extraversion, and psychoticism, were compared between adults with acne and adults without acne (Gül, A. İ., & Çölgeçen, E., 2015). The results in Table 2 show that there is a significant statistical difference between the two groups of individuals in most of the categories. This indicates that adults with acne are more likely to develop psychiatric conditions.

<table>
<thead>
<tr>
<th>Category</th>
<th>Z*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCL 90-R Global Symptom index</td>
<td>-6.87</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SCL 90-R somatization</td>
<td>-6.43</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SCL 90-R depression</td>
<td>-7.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SCL 90-R anxiety</td>
<td>-7.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EPQ neuroticism</td>
<td>-4.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EPQ extraversion</td>
<td>-1.10</td>
<td>0.269</td>
</tr>
<tr>
<td>EPQ psychoticism</td>
<td>-0.41</td>
<td>0.681</td>
</tr>
</tbody>
</table>

Table 2. Statistical comparisons of SCL 90-R and EPQ score between adults with acne and adults without acne. There is a significant difference in all SCL 90-R scores and the EPQ neuroticism score. Adapted from Gül, A. İ., & Çölgeçen, E., 2015
Specific aim and objective

We must better understand adult acne due to its high social cost and rising economic cost. A serious difficulty lies in the fact that people believe in too many different causes and home brewed treatments. Instead of consulting a professional dermatologist, they rely on either unreliable methods or misuse OTC medication. Both scenarios lead to worsening skin conditions that ultimately require more effort to resolve.

The specific objective of this study is to:

1. Compile a list of acne causes and treatment.
2. Separate misconceptions from fact.
3. Look for areas that could use further study.

This paper will try to elucidate a clear understanding of the causes and treatment for acne and remove any confusion. By doing so, we also hope to find new areas to focus research on.
CAUSES AND RISK FACTORS

The simplest explanation for acne comes from clogged hair follicles. Follicles become plugged by dead skin cells and excessive production of sebum, the oil produced from sebaceous glands, and this can lead to bacterial proliferation in the clogged follicles which causes swelling (Disease and Conditions: Acne, 2014). This progression turns the follicle into a comedo (the plural of which is comedones), also called a whitehead due to the white oily center or a blackhead, due to the oxidization of the oils when exposed to oxygen (Disease and Conditions: Acne, 2014). After turning into comedones, the clogged pores could become inflamed, further exacerbating the disease. This phase of the disease can lead to more scarring due to the formations of red papules and nodules that form (Goodman, 2006). As this illustrates, acne is not a simple disease with a singular cause. Multiple risk factors contribute to the formation and severity of acne. This section will attempt to explain several of such factors.

Hormones

Hormones play an important role in the production of acnes. Androgens, which also causes the changes associated with puberty, acts on the sebaceous glands and can cause overproduction of sebum (Mazioti et al., 2015). An early study by Lucky et al. in 1991 noted that acne prevalence is correlated with pubertal maturation in adolescent boys between the ages of 9 and 15 (see Figure 1 below). Pubertal maturation was evaluated through the scoring of pubic hair and testicular volume. They found that advanced pubertal maturity correlates with more advanced acne. This can be explained by the rising
production of free androgens that occurs during the progression of puberty. Furthermore, puberty was a better measure of acne severity than chronological age (Lucky, 1991).

Figure 1. Number of comedones and inflammatory facial acne during maturation of adolescent boys. The increase in acne strongly correlates with increase in maturation. The asterisk indicates a mean acne score that is significantly higher than the previous mean acne score. From this, pubertal stage is a better indicator of acne severity. Adapted from Lucky et al., 1991.

However, Lucky et al. did not provide any explanation for the mechanism or for the link between acne and hormones. Another study published by Lucky et al. in 1996 looked at the link between acne and hormones in girls. They found that a high level, above the 90th percentile, of certain sex hormones has a chance to lead to severe acne: dehydroepiandrosterone sulfate (DHEAS) has 77% chance, testosterone has 69% chance, estradiol (E2) has 62% chance, and progesterone has 65% chance. On the other hand, since testosterone-estrogen binding globulin (TEGB) binds to and removes testosterone and estrogen from the blood serum, a lower level, below the 10th percentile, of TEBG
have a 70% chance of leading to severe acne. The inverse is also true, lower levels of sex hormone (or higher amounts of TEBG) leads to smaller chance of developing severe acne. Since this new study only focused on adolescent girls, it is not safe to assume that similar claims can be made about adolescent boys. However, both studies found that comedones are more prevalent than inflammatory acnes for adolescents.

**Diet**

The link between diet and acne is a hotly contested one. No specific food groups have been readily identified as an absolute risk factor. However, growth hormone (GH), insulin, and insulin-like growth factor-1 (IGF-1) may cause the pathogenesis of acne (Kumari 2013). Kumari et al. has found that the interplay between these hormones may lead to overproduction of sebum during puberty. Furthermore, IGF-1 may cause an increase in androgen production, which in turn also leads to increased sebum production. Thus, Kumari et al. suggested hyperinsulinemia as a possible risk factor for acne. In this manner, any factors that may lead to insulin resistance and the subsequent hyperinsulinemia would then also become a risk factor. They included a high glycemic and high milk diet as examples of diets that may cause hyperinsulinemia. However, this does not suggest that those diets, or any particular diet, are risk factor. More rigorous testing must occur before any diet is implicated as a risk factor and Kumari et al.’s research only opens up the possibility of more research on the link between diet and acne.
Smoking

Schafer et al. found an association between smoking and acne. While smoking did not cause the acne, it certainly had an effect on the severity and prevalence of acne. They found that it is a dose dependent relationship: the more frequently someone smokes, the higher the chances that the person develops severe acne. Other factors such as age, social class, and gender did not affect the smoking and acne relationship, as shown in Table 3 below. Another study by Mills et al. suggested that smoking reduces the level of acne through nicotine’s anti-inflammation actions. However, the patients that Mills et al. examined were already taking isotretinoin, a potent antibiotic against acne, and thus the reduction of acne in those patients cannot solely be based on nicotine’s purported anti-inflammation properties (Schafer et al., 2001).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes smoked daily = 0 (reference)</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Cigarettes smoked daily = 1-10</td>
<td>1.36</td>
<td>0.79-2.35</td>
</tr>
<tr>
<td>Cigarettes smoked daily = 11-20</td>
<td>1.85</td>
<td>1.15-2.99</td>
</tr>
<tr>
<td>Cigarettes smoked daily &gt; 20</td>
<td>2.11</td>
<td>1.14-3.92</td>
</tr>
<tr>
<td>Social class</td>
<td>0.88</td>
<td>0.76-1.02</td>
</tr>
<tr>
<td>Age</td>
<td>0.68</td>
<td>0.62-0.75</td>
</tr>
</tbody>
</table>

Table 3. Regression models for acne prevalence and cigarette consumption. The odds of having acne are calculated for various variables. Increasing the amount of cigarettes consumed increases the chances for acne. Social class and age do not contribute to a higher chance of developing acne since the odds are less than 1. Adapted from Schafer et al., 2001.

Environment

The environmental factors are those that a person will come into contact with daily. The most obvious of such factors is the weather. Stathakis et al. found that hot and
humid environments adversely affect those with acne. They attributed the cause to ductal hydration which may lead to worsening of a clogged hair follicle. Mazioti et al. found that the chemicals permeating the environment in western civilizations might also contribute to the higher acne incidence. They believe that chemicals with androgen agnostic like properties can activate androgen receptors which would lead to increased sebum production.

**Biology**

Biological factors are the final risk factors discussed and this term includes age, race, and stress. Stathaskis et al. reported that acne can start pre-puberty as comedones and peaks in severity in adolescents. However, new studies have shown that acnes can continue well into adult life, with a 1% (male) and 5% (female) incidence in those over 40 and a 8% (male) and 18% (female) incidence in those over 25 (Goodman, 2006). Different race do have a difference in severity of acnes. Lucky et al., in 1991, found that black adolescent boys have worse acne than their white counterparts. However, they failed to report the same findings in girls. A much older study by Hamilton et al. done in 1964 showed that white Americans had a higher incidence of acne than their Japanese counterparts. Stathaskis et al. found that stress does not cause acne, but can aggravate existing acne. They suggested that the reported flare ups in acne is due to an anxiety induced combination of psychological misconception and the physical action of picking at and aggravating existing acne.
TREATMENT

Many treatment options exist for acne today. Since there are so many different causes for acne, each treatment is able to target a specific causative factor. No one treatment is significantly better than another treatment. Some treatments, such as antibiotics and topical retinoids, are commonly used together. The frequency and severity of treatment varies and depend on the severity of the disease and other biological factors in the patient. This section will attempt to elucidate the main treatment options, how they work, and their drawbacks for acne.

Oral Antibiotics

Oral antibiotics are commonly prescribed as a first line of defense against acne. It specifically targets Propionibacterium acnes (P. acnes), the main bacteria that proliferate in clogged hair follicles. Oral antibiotics can suppress acne by either directly reducing the bacteria’s proliferation or by anti-inflammatory mechanics (Amin et al., 2007). However, overuse of antibiotics has led to the rise of antibiotic resistance. This has necessitated even stronger antibiotics, using alternative medicine, or combining the use of antibiotics with other treatment options (Amin et al., 2007). A problem common to all antibiotics is poor compliance. Due to the frequent dosage and long time span of the medication, some patients will deviate from the prescribe medication route, which leads poor treatment, resurgence of acne, and contributes to the proliferation of antibiotic resistance bacteria.

Table 4 summarizes the list of discussed oral antibiotics.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Formulations</th>
<th>Usual Oral Dosage</th>
<th>Cost of 30-day Supply (<a href="http://www.drugstores.com">www.drugstores.com</a>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>250, 500 mg capsules</td>
<td>125-250 mg QID or 250-500 mg BID</td>
<td>$7.99 for 30 tabs</td>
</tr>
<tr>
<td>Sumycin</td>
<td>250, 500 mg tablets</td>
<td>same as above</td>
<td>$7.99-$20.40 for 30 tabs</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>20, 50, 75, 100 mg IR 75, 100 ER capsules</td>
<td>100 mg daily</td>
<td>$8.99 (20 tabs)-$33.99 (30 tabs)</td>
</tr>
<tr>
<td>Adoxa</td>
<td>50, 75, 100 mg tablets</td>
<td>100 mg daily</td>
<td>$171.15 for 30 tabs</td>
</tr>
<tr>
<td>Doryx</td>
<td>75, 100 mg ER enteric-coated tablets</td>
<td>100 mg daily</td>
<td>$158.36 for 30 75-mg tabs</td>
</tr>
<tr>
<td>Oracea</td>
<td>40 mg capsules (30 mg IR + 10 mg delayed release)</td>
<td>40 mg PO q am</td>
<td>$139.99</td>
</tr>
<tr>
<td>Periostat</td>
<td>20 mg tablets</td>
<td>20 mg BID</td>
<td>$92.99 for 60 tabs</td>
</tr>
<tr>
<td>Vibramycin</td>
<td>50, 100 mg capsules 25, 50/5 ml suspension or syrup</td>
<td>100 mg daily</td>
<td>$110.86 for 20 tabs</td>
</tr>
<tr>
<td>Minocycline</td>
<td>50, 75, 100 mg capsule 75 mg tablet</td>
<td>100 mg BID</td>
<td>$46.00 for 60 tabs</td>
</tr>
<tr>
<td>Minocin</td>
<td>50, 100 mg capsule</td>
<td>100 mg BID</td>
<td>$528.82 for 60 tabs</td>
</tr>
<tr>
<td>Solodyn</td>
<td>45, 90, 135 mg ER tablets</td>
<td>45-135 mg daily</td>
<td>$452.39</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>250, 500, 600 mg tablets</td>
<td>500 mg TIW x 4 wks (No recommended dose for acne)</td>
<td>$175.20</td>
</tr>
<tr>
<td>Z-pak</td>
<td>250 mg tablets</td>
<td>500 mg x 1 day, then 250 mg daily x 4 days</td>
<td>$53.76</td>
</tr>
<tr>
<td>Tri-pak</td>
<td>500 mg tablets</td>
<td>500 mg x 3 days</td>
<td>$50.74</td>
</tr>
<tr>
<td>Erythromycin base</td>
<td>250, 500 mg tablets, enteric-coated capsules</td>
<td>250-500 mg q6h</td>
<td>$34.17-$35.96</td>
</tr>
<tr>
<td>E-mycin</td>
<td>250, 333 mg enteric-coated tabs</td>
<td>333 mg q6h</td>
<td>$50.97</td>
</tr>
<tr>
<td>Ery-Tab</td>
<td>250, 333, 500 mg enteric-coated tabs</td>
<td>333 mg q6h</td>
<td>$32.73</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>100, 200 mg tabs</td>
<td>100 mg TID or 300 mg BID</td>
<td>$51.36-$102.73</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>80/400, 160/800 (DS) mg tabs</td>
<td>80/400 mg daily or DS tab daily</td>
<td>$8.99</td>
</tr>
<tr>
<td>Bactrim</td>
<td>80/400, 160/800 tabs</td>
<td>as above</td>
<td>$32.49-$44.99</td>
</tr>
<tr>
<td>Septra</td>
<td>400-80 mg tablets</td>
<td>as above</td>
<td>$43.74-$57.48</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Variable</td>
<td>Not commonly prescribed</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Variable</td>
<td>Not commonly prescribed</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. List of common oral antibiotics.** This table lists common oral antibiotics, their other names, available dose, the frequency of usage (QID is 4 times a day, TID is 3 times a day, BID is twice daily, PO is taken orally, TIW is 3 times a week, ‘*’ denotes sub-antimicrobial), and price. Cephalosporin is not discussed in this paper since it is rarely used. Adapted from Amin et al., 2007.
**Tetracycline**

Tetracycline and its derivatives are the first prescribed medication for acne (Amin et al. 2007). They are not only antimicrobial that inhibit bacterial growth by suppressing protein synthesis on the 30S ribosomal subunit, but also anti-inflammatory through the down-regulation of pro-inflammatory cytokines and suppression of reactive oxygen species formation (Amin et al., 2007). These drugs also decrease sebum production through the inhibition of phospholipase A (Amin et al, 2007). In all, this drug acts against acne through the combined effects of decreasing bacteria infiltration of the pores, reducing inflammation associated swelling, and lessening the pore clogging by sebum. Side effects range from moderate to serious. Moderate side effects include gastrointestinal distress (which manifests as diarrhea, vomiting, and indigestion), intracranial hypertension, and photosensitivity while serious side effects include esophageal ulceration, vaginal fungal infection, and severe cutaneous reaction such as Steven-Johnson syndrome, a necrosis of the skin (Amin et al., 2007). Pregnant women should also avoid tetracycline as it discolors fetus’s enamel (Amin et al., 2007).

**Doxycycline**

Doxycycline is a broad spectrum antibiotic that is a derivative of tetracycline; however, it is more lipophilic than tetracycline (Amin et al., 2007). The lipophilic property of these drugs allows it to penetrate the sebaceous gland so a more lipophilic drug can better act against the bacterium. It has the same side effects as tetracycline, although it is more likely to produce phototoxic effects (Amin et al. 2007). A study by
Skidmore et al. in 2003 showed that doxycycline, at a dosage below needed for antimicrobial effects, had an anti-inflammatory effect. The same study also noted that a sub-antimicrobial dosage is effective in treating moderate acne. Thus, a sub-antimicrobial dose of doxycycline should be investigated as a possible oral antibiotic treatment of acne that would not contribute to the rise of antibiotic resistance bacterium.

**Minocycline**

Minocycline is the latest edition of tetracycline derivatives. It is as effective as its predecessors, less resisted by *P. acnes*, and has been noted to produce a faster and more sustained result, possibly a result of its much higher lipophilic property and thus higher penetrance into the sebaceous glands (Amin et al., 2007). Garner et al. in a 2003 study has shown that despite been faster and more sustained, minocycline is not better than its predecessors at clearing up acne. It is also more expensive and has more side effects, including side effects encountered by tetracycline (Amin et al., 2007). Not only can it cause lupus, hepatitis, serum sickness, vasculitis, and pneumonitis, but some death have also been associated with minocycline (Garner et al., 2003). However, Garner et al. has noted that the chances of meeting these side effects are extremely small. Thus, usage of this drug should not be discouraged despite these drawbacks.

**Macrolides**

Macrolides are a wide spectrum oral antibiotic with good oral absorption and lipid solubility; they act by inhibiting protein synthesis via binding to 23S rRNA in the 50S
ribosomal subunit (Amin et al., 2007). One such macrolide, erythromycin, has a similar efficacy as tetracycline except it can also be used by pregnant women (Amin et al. 2007). However, overuse has led to increasing resistance to erythromycin so other macrolides are necessary for an effective treatment against acne. Azithromycin is the new derivative of erythromycin with 10 times the uptake of erythromycin, a much longer half-life, and fewer gastrointestinal problems (Amin et al. 2007). Amin et al. has noted that multiple studies have proven the efficacy of azithromycin to be similar or better than tetracycline and doxycycline. Therefore, the rapidness of this drug, longer half-life, and efficacy means that it can be sustained in the body with fewer doses, which can lead to an improvement in compliance.

Trimethoprim +/- Sulfamethoxazole

Trimethoprim, with or without sulfamethoxazole, should be used when the patient fails to respond to tetracycline derivatives and macrolides (Amin et al. 2007). It is not the first prescribed medication since it has much more severe side effects than the other drugs. Side effects include blood disorder, Steven-Johnson syndrome, and renal disease (Jick and Derby, 1995). However, Jick and Derby also found that the incidence of the serious side effects were extremely low with all of them occurring at a rate of less than 8 out of 100,00. Layton et al. found that most patients who fail to respond to tetracycline or macrolides not only because of antibiotic resistance bacterium, but also because of excessive sebum production which blocks the drugs entry into the sebaceous gland. They
also noted that excessive sebum production does not block the actions of trimethoprim, which makes it a good alternative when traditional antibiotics fail.

**Flouroquinolone**

Flouroquinolone, derived from quinolones, is a broad spectrum antibiotic that prevents bacterial DNA synthesis by inhibiting DNA gyrase and topoisomerase IV (Amin et al., 2007). While it is able to act on *P. acnes*, it is also used against many other diseases such as uncomplicated and complicated skin infections (Amin et al., 2007). As such, it should be used sparingly against acne since its overuse could result in antibiotic resistance in many of its other targets. Amin et al. also noted that not much research has been done on the efficacy of flouroquinolones so that is also an issue to consider when prescribing the drug.

**Isotretinoin**

Isotretinoin is not an antibiotic but rather a retinoid that is usually taken orally. It is used against severe, nodular acne by reducing sebum output (Drugs and Medication). Normally, this drug should be used as a last defense measure due to its toxic side effects. As of 2005, this drug is regulated and only those who have signed and registered with the iPledge program may be prescribed the drug (Drugs and Medication). In particular, pregnant women or women who plan on becoming pregnant should avoid it due to its high teratogenic properties (Drugs and Supplements, 2015). A full list of its side effects is too long to be listed here, so only common complications and a few rare but major complications will be listed. Common side effects are the following: joint pain, dry
mouth, lip and eyelid inflammation, nosebleed, stomachaches, skin irritation, photosensitivity, and mild hair loss (Drugs and Supplements, 2015). Some serious complications include, but are not limited to, the following: suicidal thoughts, mood swings and depression, bleeding in the gum, severe gastrointestinal distress, and rectal bleeding (Drugs and Supplements, 2015). It has also been implicated in hepatitis and glomerulonephritis (Isotretinoin, 2015). Despite its toxicity, it should be considered for extremely stubborn forms of acne or if all other treatment plans fail and only when he physician deem that isotretinoin’s benefits outweighs the side effects.

**Topical Treatment**

Topical treatments target the bacteria, *P. acnes*, skin cells, or inflammation. Different types of topical medication do different things and they are combined with oral antibiotics to maximize efficacy. Unlike antibiotics, topical treatments (except for topical antibiotics) do not cause antibiotic resistant bacteria. However, like antibiotics, topical treatments also have compliance issues. Kellet et al. found that patients have a higher compliance if the medication is gel based, not cream or lotion based, can be kept at room temperature for a long period of time, can be applied directly with finger, and is only applied once a day instead of multiple times a day.

**Retinoids**

Retinoids is the basic topical treatment that should be used in almost all but the most extreme cases since it has both comedolytic and anti-comedogenic actions (Gollnick, 2015). Since inflammatory acne is formed from comedones, retinoids can
effectively serve as a first line of defense against more severe forms of acne by treating severe acne’s precursors. It does so by normalizing the differentiation and hyperproliferation of follicular epithelium and also through some anti-inflammatory effects (Gollnick, 2015). This prevents the accumulation of dead skin cells, which can help prevent the formation of comedones. Side effects of topical retinoids include erythema, scaling, dryness, skin irritation, and transient phase flare up during treatment (Gollnick, 2015).

**Topical antibiotics**

Topical antibiotics act in the same way as oral antibiotics in that they both target *P. acnes*. Clindamycin, in particular, also has anti-comedogenic action through anti-inflammatory effects (Gollnick, 2015). However, topical antibiotics face the same problems as oral antibiotics in that bacterium are developing resistance to it. To combat antibiotic resistant strains, topical antibiotics are often used with together with retinoids (Gollnick, 2015).

**Benzoyl Peroxide (BPO)**

BPO’s work in the same way as antibiotics in that they are also anti-microbial with weak anti-inflammatory properties (Gollnick, 2015). A study by Sagransky et al. showed that BPO, unlike antibiotics, does not cause resistance in bacterium. The same study also found side effects of skin irritation and dryness, allergic reactions, and bleaching of hair and clothing.
**Fixed Dose**

Fixed dose regimens combine an antimicrobial component with a topical retinoid component. As shown below by Table 5, a single application of the medication can target 3 factors that cause acne. Furthermore, combining the medications together can increase compliance since now the patient is only require to apply a single medication once per day instead of multiple treatments multiple times per day. As shown below by Figure 2, a fixed dose regimen has better compliance and treatment effect than separate applications of both a retinoid and antimicrobial medication.

<table>
<thead>
<tr>
<th>Topical treatment</th>
<th>Sebum production</th>
<th>Keratinization</th>
<th>Bacterial colonization</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoids</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>BPO</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>(+)</td>
</tr>
<tr>
<td>Retinoid/antimicrobial combination</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

**Table 5. Pathogenic targets of topical treatment.** This table summarizes the different treatments and their targets. ‘-’ indicates no effect, ‘+’ indicates mild effect, and ‘++’ indicates strong effect. Adapted from Gollnick, H.P.M., 2015.
Figure 2. Comparison of adherence and effectiveness between fixed dose and separate dose. Both (a) and (b) compare the differences between a fix dose of both retinoid (tretinoin) plus antimicrobial (clindamycin) and a separate application of both tretinoin and clindamycin. Part (a) shows that the fix dose has a better adherence than separate application while part (b) shows that the fix dose is more effective at reducing acne. Adapted from Gollnick, H.P.M., 2015.

**Hormone Treatment**

Hormonal therapy should only be considered when all other options are exhausted. Furthermore, this therapy is designed for women, and it is unknown what effects hormone therapy will have on men. Women benefit more from this therapy as there are much more adult women who suffer from a severe form of acne than men (Perkins et al., 2012). According to Thiboutot, signs of severe form of acne include
sudden flare ups, hirsutism (excess facial hair growth on women), irregular menstrual periods, and hyperandrogenism symptoms. Since hormones contribute greatly to the formations of acne, Thiboutot also suggests performing an endocrine evaluation and check for DHEAS, testosterone, free testosterone and luteinizing hormone/follicle stimulating hormone (LH/FSH) levels. It is necessary to check for high LH/FSH levels since an elevated serum count could stimulate the ovary into overproducing androgens. However, despite normal levels of hormones, there might still be an underlying endocrine basis for the acne problem. If the physician decides on hormonal therapies and to reduce androgen levels, then there are 3 ways to approach the problem: androgen receptor blocker, adrenal androgen production blocker, and ovarian androgen blocker.

**Androgen Receptor Blocker**

These drugs block the action of androgens on the sebaceous glands (Thiboutot, 2001). One class of androgen receptor blocker is spironolactone. It helps decrease sebum production rate through reducing free circulating testosterone and competitive binding of the receptors on the sebaceous glands and only a low dosage twice a day can achieve the intended effects (Husein-Elahmed, 2015). Side effects include irregular menstrual cycle, and breast tenderness (Thiboutot, 2001). Another drug is cyproterone acetate which suppresses gonadotropins and blocks testosterone receptors (Husein-Elahmed, 2015). Finally, flutamide can also be used. It does not cause any menstrual irregularities, however, it can cause severe gastrointestinal disorder and possibly liver failure so the liver should be monitored closely (Husein-Elahmed, 2015).
**Adrenal Androgen Production Blocker**

Glucocorticoids can be used to block the production of androgens. This therapy is commonly used along with oral contraceptives (OC) (Thiboutot, 2001). Late onset adrenal hyperplasia can cause an overproduction of androgen precursors. This therapy is intended to suppress the adrenal glands so that these precursors do not build up and become excess DHEAS. Successful therapy will decrease serum DHEAS levels (Thiboutot, 2001).

**Ovarian Androgen Blocker**

Blocking the cyclical release of LH/FSH with gonadotropin releasing agonist can interrupt ovulation; however, this will also prevent the formation of estrogen which would lead to menopausal syndromes (Thiboutot, 2001). OC is another option. Generally, ethinyl estradiol and a progestin are used to suppress sebum production (Thiboutot, 2001). Many different combinations with different dosage exist to serve different functions (Husein-Elahmed, 2015).

**Laser and Light Based Treatment**

Laser and light therapy for acne are being used for treatment in addition to the traditional treatment options listed above. While oral medication, topical treatment, and hormone therapy are effective, they are only as effective as the patient’s compliance. While not specifically discussed in this paper, those forms of treatment often take months to be effective (Goodman, 2006). Furthermore, some patients may experience unwanted side effects or allergic reactions to those drugs. Therefore, laser and light based
treatments provide a fast and safe alternative to taking care of the acne problem (Reena & Karthika, 2013). Like previous treatment options, laser and light based therapy targets either *P. acnes*, the sebaceous glands, or both. Table 6 below shows the various forms of therapy and their intended targets.

<table>
<thead>
<tr>
<th>Target</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. acnes</em></td>
<td>• UVA/UVB</td>
</tr>
<tr>
<td></td>
<td>• Blue light</td>
</tr>
<tr>
<td></td>
<td>• Blue and red light combination</td>
</tr>
<tr>
<td>Sebaceous gland</td>
<td>• PDT with ALA</td>
</tr>
<tr>
<td></td>
<td>• Infrared laser</td>
</tr>
<tr>
<td></td>
<td>• Radiofrequency</td>
</tr>
<tr>
<td>Both</td>
<td>• PDL</td>
</tr>
<tr>
<td></td>
<td>• KTP laser</td>
</tr>
<tr>
<td></td>
<td>• IPL</td>
</tr>
</tbody>
</table>

**Table 6 List of light and laser treatments and their targets.** Treatments can target either the bacteria, the sebaceous glands, or both. Adapted from Reena & Karthika, 2013.

Treatments that target the bacteria follow a similar course of action. Like the traditional treatments, the goal is to kill existing bacteria and prevent further proliferation. Light and laser therapies target porphyrins that accumulate in the bacteria (Reena & Karthika, 2013). Porphyrins readily absorb light at the UV to blue spectrum and the excitation by these wavelength causes the porphyrins to generate damaging free radicals which kills off the bacteria (Elman & Lebzelter, 2004). Reena and Karthika have also noted that light of any wavelength can also be absorbed by the bacteria, causing excitation, if the energy output is large enough. Therapies that target the sebaceous glands all have the same goal of reducing sebum output (Reena & Karthika, 2013).
UVA/UVB

There have been conflicting reports regarding the efficacy of sunlight on the treatment of skin and acne. Some reports that UV light can help with skin rejuvenation and can help alleviate acne problems while others believe that UV light is 100% harmful (Reena & Karthika, 2013). However, UV light is known to be carcinogenic, and any benefits that it can derive must be weighed against its carcinogenic nature.

Blue + Red Light

While blue light is better absorbed by the bacteria, it has poor skin penetrance (Reena & Karthika, 2013). Red light, on the other hand, can penetrate deep into the sebaceous glands and has also been shown to have anti-inflammatory properties (Reena & Karthika, 2013). As stated above, as long as the energy output for the red light is high enough, it can be absorbed by the bacteria. Thus, many different combinations of blue and red light have been used in treating acne. Studies have shown that a combination of both light is better than using blue light alone, but no studies have been longer than 12 weeks and relapse of the acne is possible after discontinuing therapy (Pei et al., 2015).

PDT with ALA

Photodynamic therapies require the application of ALA, which is absorbed and metabolized by the sebaceous gland to produce protoporphyrin IX (Reena & Karthika, 2013). Protoporphyrin IX is activated by light and produce singlet oxygen and free radical species, which damages the sebaceous gland and surrounding bacteria (Reena &
Karthika, 2013). This may seem like a good therapy that also targets *P. acnes* but it is listed as only targeting sebaceous glands in table 6 for reason. The extent of damage that this therapy causes to the bacteria depends on a host of variables such as concentration of applied ALA, temperature, and amount of available of oxygen (Reena & Karthika, 2013). Thus, it is safer to concluded that majority of its actions against acne comes from decreasing sebum output.

**Infrared lasers**

Infrared lasers consist of 1540 nm diode lasers and 1540 nm erbium glass lasers that injure sebaceous glands by heating up the surrounding water (Reena, Kathika, 2013). The injured sebaceous glands produce less sebum which leads to a reduction in acne. Due to the safety and efficacy of the 1540 nm diode laser, it is a commonly prescribe treatment method (Jih & Kimyai-Asadi, 2007). Though a few tests have revealed its efficacy, the 1540 nm erbium glass laser has not been stringently tests and requires more research (Pei et al. 2015).

**Radiofrequency**

Radiofrequency have been combined with intense pulsed light therapy (Jih & Kimyai-Asadi, 2007). While it was able to reduce acne count, the mechanism is unknown but speculated to be though reducing sebaceous gland inflammation; furthermore, it was also associated with erythema, burning, and skin irritation (Reena & Kirthaka, 2013).
Due the mix results and lack of study, more research is needed to determine its efficacy and mode of action.

**PDL**

Pulse dye laser are 585 nm yellow lasers not only targets porphyrins, but also inflamed vasculatures and eliminate them through photothermolysis (Reena & Karthika, 2013). Thus, this therapy can treat acne not only through killing off the bacteria, but also through reducing the inflammation associated with acne. However, studies have also shown that this treatment may have no effect on reducing *P. acnes* proliferation or sebum output (Jih & Kimyai-Asadi, 2007). Reena and Karthika also reports on conflicts over its purported efficacies since many studies were also done in conjunction with other treatments.

**KTP laser**

Potassium titanyl phosphate lasers use 532 nm green light since it penetrates better than blue light and can also activate the porphyrins in bacteria (Reena & Karthika, 2013). This technique is easier than the blue and red light therapy since it does not require mixing a combination of two lights. It also causes tolerable, non-specific injuries to the sebaceous glands (Reena & Karthika, 2013). This allows the therapy to reduce sebum output though the exact mechanism is unkown.
**IPL**

Intense pulse light uses a broad spectrum of non-coherent light (between 500 to 1000 nm) that is filtered to provide irradiation by a desired wavelength (Reena & Karthika, 2013). In addition to destroying porphyrins, Pei et al. noted that it can also destroy blood vessels that lead to sebaceous glands. It may be possible to lower sebum output by reducing sebaceous gland’s blood supply. However, it can cause erythema, blistering, pain, and irritation so application of only this therapy is not recommended and it may be better to combine it with other therapies (Pei et al. 2015). As noted above, radiofrequency therapy have been combined with IPL to produce mixed results.
MISCONCEPTIONS

Misconceptions about acne can range from the simple to the insane. What is even more concerning than patient believing incorrect ideas about acne is that even physicians can be incorrect. A study by Brajac et al. showed that only 9% of family physicians knew about some of the serious side effects of isotretinoin and only 21% of family physicians answered questions regarding oral antibiotics correctly. They also found that only 53% of physicians considered acne as a serious disease while only 56% believe treatment is necessary. As studies by Aktan et al., Isaacsson et al., and Khunger & Kumar have shown, acne has a debilitating effect on people’s psyche as it can cause anxiety, depression, and dissatisfaction with life. It is dangerous for physicians to not take acne seriously and disregard the need for treatment. This could result in physical damage to the patient through scarring and psychological damages. This Brajac et al.’s study, along with Goodman’s paper showed family physicians as the foremost source of information regarding acne. Physicians must be clear about the truth and myths surrounding acne in order to Furthermore, in both studies, patients stated that they received information about acne from the media, family members, and friends. Therefore, there is an even greater importance for physicians to be clear about facts about acne in order to prevent the patient from learning and acting on incorrect information. Due to the wide range of mistaken beliefs about acne, this paper will only touch on documented cases.
Diet

One of the most enduring myths about acne is diet. Oily food, fatty food, and chocolate are some of the most well cited cause of acne (Goodman, 2006). However, no conclusive link has been found between diet and acne. Even the link between hyperinsulinenemia, milk, and acne (as noted above in the diet section of causes and risk factor) is a tenuous one.

Hygiene

Many people believe that a poor facial washing and maintenance can lead to acne. The dirt that they attribute to the brown discoloration in pimple is actually the oxidization of sebum (Goodman, 2006). In fact, excessive face washing can actually lead stripping the skin of essential oils, leading to irritation and dryness (Zaidi, 2009). Some people also believe that leaving cosmetics on for too long will exacerbate acne. While that may be true for some products, most products produced now are water based, do not block pores, and some even have benzoyl peroxide mixed in to help with acne (Zaidi, 2009). While it may be safe to assume that most cosmetic are safe to use with acne, a simple check can verify the safety of the product.

Disease Course

Brajac et al,’s study found that most people believe that acne is an adolescent disease that clears up upon reaching adulthood. In addition, people also believe that the disease will resolve quickly. The unfortunate truth is that acne can persists well into adulthood. Collier et al. and Khunger & Kumar found that the disease can persist into the
late a person’s late twenties and is extremely prevalent in women. Whether if it is due to genetic, environmental factor, or some other causes, patient need to prepare for the worst and face a long battle against acne. Furthermore, they must be wary of any acne quick fixes marketed by the media. Treatment last for between 4 to 6 month and there may be need for repeated treatment after the initial one ends (Zaidi, 2009).
FUTURE RESEARCH

Though many studies exist about the cause and treatment of acne, we can see that there are still gaps in the literature. This section will attempt to formulate some new research that can help fill those gaps.

Treatment

Some treatments have been exhaustively studied while others are only beginning to become of interest. More studies need to focus on the new treatment options such as flouroquinolones, radiofrequency and 1540 nm erbium glass laser. The efficacies of new treatment must not only be proven, but also compared to other treatments which have already received a plethora of studies. Furthermore, treatments with studies that gave mixed results should also be revisited in order to provide a clearer result.

Stress

Stress has been implicated to aggravate existing acne through psychological effect or from unconscious picking at acne. However, studies have not examined if there are any definitive link between stress and acne. Stress can induce inflammatory cytokines and production of cortisol, which can also cause inflammation. Thus, it would be worth looking to see if a mechanism of stress induced inflammation leading to acnes exists.
Culture

In order to better understand why some of these misconceptions persist and why some people believe them, it is necessary to look at different culture’s view on acne. Separate research exists on epidemiological studies of acne in certain regions, but no concrete or all-encompassing study has been done. It would be useful to use the same set of questions and survey and apply them to different demographics to see how different cultures process information about acne.

Diet

Though no links have been discovered between diet and acne, we should not automatically discard diet when thinking about acne. Cordain et al.’s study showed that there must be more than a genetic basis for the difference in acne prevalence. Whether this difference is diet or some other factor is unknown. Furthermore, there is also a paucity of data about diet in general and this area is worthy of a closer look in order to provide more information about acne.
CONCLUSION

Acne is a complex disease with many contributing factors. Treating it involves targeting one or more of its many causative factors. While multiple treatments exist, the treatments are only as good as the patient using them as many of these treatments suffer from poor compliance. Furthermore, this disease is complicated by the multitude of misconceptions and myth surrounding it. In order to properly combat this disease, patients and physicians should be properly educated about acne's facts and fiction. More research is needed to clarify some of acne’s many confusing points.
REFERENCES


