Yes, you CAN prescribe Isotretinoin (Accutane)!
Value added prescribing for NPs
Meara Henley, DNP, RN, CPNP-PC, PMHS

Speaker Introduction
• Dr. Meara Henley is a PNP with 11 years of experience in primary care with a focus on adolescent health. She has built regional adolescent practice at her current clinic in San Marcos, Calif. She has been the chair of the Adolescent Health Care SIG for the last six years and previously served as the SIG's treasurer/secretary.

Disclosures
Meara Henley has no financial or other disclosures to report

Learning Objectives
1. Review AAP recommended acne treatment guidelines
2. Increase comfort level with step wise approach for acne treatment
3. Recognize and define available therapies for acne treatment
4. Identify and describe which patients are candidates for Isotretinoin
5. Describe and recognize the iPledge system and how to register/use
6. Identify information about the safety, efficacy, and process to prescribe and monitor Isotretinoin usage
7. Feel empowered to consider prescribing Isotretinoin

What is acne?
• Multifactorial
  • Inflammatory disease
  • Affects pilosebaceous follicles
  • Sebaceous hyperplasia
  • Increased androgen levels
  • Alterations in follicular growth/differentiation
  • Colonization by Propionibacterium acne
  • Consequent immune response -> inflammation
  • Possibly induce keratinocyte hyperproliferation
  • Still not well understood

Teen’s thoughts on Acne
• Not something that can easily be hidden
• Teens don’t always tell how much it bothers them
• Recommend always asking teens if they want treatment
• Upwards of 85% of teens affected to some degree
• Significant impact on self esteem
• Teens rate highest quality of life measure
• “No one ever offered me treatment”
  • Teens unaware they can have treatment in primary care
Preadolescent acne
- May be first sign of puberty
- Normal adrenarche and testicular/ovarian maturation
- Most common = comedones in "T-zone"
- Early presentation may include comedones of the ear
- History and physical
  - Signs of excess androgens?
  - If severe, consider PCOS
- Treatment similar to adolescents
- Treat early and treat often!

Review of Nomenclature
- Closed comedones
  - Whiteheads (closed clogged pores) - Non inflammatory
- Open comedones
  - Blackheads (open clogged pores) - Non inflammatory
- Pustules
  - Papules with pus at their tips - Inflammatory
- Papules
  - Small red, tender bumps - Inflammatory
- Cysts
  - Painful, pus-filled lumps beneath the surface of the skin
- Nodules
  - Large, solid, painful lumps beneath the surface of the skin

How would you describe these lesions?
1. Open comedones + cystic lesions
2. Open and closed comedones + nodules
3. Closed comedones + cystic lesions
4. Open and closed comedones + nodular and cystic lesions

A word about blemish extractors
- Probably best to avoid extractions at home
- Extractors can accidentally push contents into skin
  - More inflammation
  - Increased infection potential
  - More scarring
- Best for blackheads
  - If a pimple is "red and juicy" more potential for complications
How does acne medication work?

- Benzoyl Peroxide (BP/BPO)
  - Free radicals oxidize proteins in cell wall
  - Limits bacterial resistance
  - Breaks down cell wall
  - Increases efficacy of retinoids in combo meds
  - Mild anti inflammatory and mild comedolytic properties alone
- Retinoids (Retin-A, Tazorac, Differin)
  - Desquamation of the follicular epithelium
  - Prevent formation of microcomedones
  - Precursor to acne lesions
  - Clears current microcomedones
  - Direct anti inflammatory activity

Topical antibiotics (Clindamycin)
- Not recommended alone

Systemic antibiotics (Minocycline/Doxycycline)
- Lipophilic follicular penetration
- Affects P. acnes production
- Dapsone
  - Antimicrobial and anti inflammatory
  - Most effective with inflammatory lesions (esp with Retinoid)
Hormonal therapy (OCPs)
- Suppress ovarian androgen production
- Decrease sebum production

Over the counter treatments

- Antibacterial washes generally not effective
  - Benzoyl Peroxide most likely to be successful
  - Salicylic washes mildly effective
  - BP is better
- Pre-packaged acne systems (Proactiv, etc)
  - Facial toners common
  - Can cause irritation
  - ie Salicylic wash + BP OTC + BP wash -> Irritation/Dryness
- Mild acne
  - OTC BP product will likely work well

A case study

AM, an 11 year old female, is here with her mother. AM has not had a period yet, but for last few months has had several areas on cheeks and forehead with mildly red pimples. AM's mother feels that AM's acne doesn't need treatment because “all kids have acne”. The family is uninsured.

What should we do?
1. Educate family that AM’s acne is likely a sign of puberty
2. Educate family that BP OTC would be best tx for patient
3. Offer BP Rx because it’s normally inexpensive
4. Discuss treating early/treating often with Mother
5. All of the above

How Isotretinoin works

- Synthetic Vitamin A
- Lipophilic -> take with food for best absorption
- Targets all factors in acne production
  - Reduces sebaceous gland activity
  - Reduces/eliminates activity of P. acnes
  - Calms cell production inside pores
Acne Classification and Treatment

Mild Acne - Comedonal or Inflammatory Mixed
(<20 lesions)

Mild Acne Treatment Recommendations

- Initial (individual medications)
  - Benzoyl Peroxide (BP/BPO)
  - Topical Retinoid (Retin-A, Differin, Tazorac)

OR

- Topical Combination Therapy
  - BP + Topical Antibiotic
  - Topical Dapsone can be used in place of topical antibiotic
  - Retinoid + BP
  - Retinoid + BP + Topical Antibiotic

Inadequate Response

- Assess Adherence!
- Add BP or Retinoid if not already prescribed
- Change topical retinoid concentration/type/formulation
- Change topical combination therapy

Assess Adherence

- Is patient taking as prescribed?
- Were there side effects?
- Is patient skipping days?
- Did they give up?
- Value of education before prescribing
  - Acne is stubborn
  - May get worse before it gets better
  - May have dryness (drop to every other day and work back up)
  - Preventing future scarring + treating current pimples
- 1 month initial follow up
  - Might be too soon to see full effects
  - Improves adherence and provides support

Additional Treatment Considerations

- Previous treatment/history
  - What worked or what didn’t?
- Cost/Insurance coverage
  - Medicaid versus Private
- Ease of use/Complexity
  - QD versus BID
- Active scarring
  - Treat early and often
Moderate Acne - Comedonal or Inflammatory Mixed
(20 – 100 comedones or 15 – 20 inflammatory lesions)

Moderate Acne Treatment Recommendations

- Topical Combination Therapy
  - Retinoid + BP
  - Retinoid + (BP + Antibiotic)
  - BP + (Retinoid + Antibiotic)

OR

- Oral Antibiotic + Retinoid + BP
- Oral Antibiotic + Retinoid + Topical Antibiotic + BP

Inadequate Response

- Assess Adherence!

THEN

- Change topical Retinoid concentration/type/formulation
- Change topical combination therapy
  and/or

- Add or change oral antibiotic
- Consider hormonal therapy

OR

- Consider Oral Isotretinoin

Severe Acne - Inflammatory or Mixed and/or Nodular
(> 5 cysts, > 100 comedones, or > 50 inflammatory lesions)

Severe Acne Treatment Recommendations

- Initial
  - Oral antibiotic + Topical Retinoid + BP (with or without topical antibiotic)
  - Topical dapsone may be used instead of topical antibiotic

OR

- Isotretinoin

Inadequate Response

- Assess Adherence!
- Change antibiotic
- Consider Isotretinoin
- Consider Hormone therapy
What type of Acne is this?

Which type of Acne is this?
- What Acne?!
- Mild
- Moderate
- Severe

What treatment should we try FIRST?
- BP
- BP + Retin A
- BP + Retin A + Topical Clindamycin
- OCPs
- Isotretinoin

That didn’t work! What now?
- Minocycline + Differin
- BP + Differin + OCPs
- BP + Retin A + Clindamycin + Minocycline + OCPs
- Isotretinoin
- They are all possibilities

The Case for Isotretinoin in Primary Care
- Relationship with patient and family already established
- Increased patient satisfaction
- Ability to discuss at multiple visits
- Long wait times for Dermatology
- Value added in primary care
- PCPs are no strangers to prescribing medications with risks
  - Opioids, Diabetes, Seizure meds
- Well suited to manage laboratory, contraceptive and monitoring
- iPledge system allows PCPs to prescribe

Isotretinoin
Who Needs Isotretinoin?
- Moderate to severe acne
- Nodular and cystic lesions
- Has tried and failed step wise approach
  - Usually required by insurances before rx
  - Scarring (physical and emotional)
  - Isotretinoin can be considered for moderate acne
- Back and chest acne

Introducing Isotretinoin
- Lots of negative information out there
- Initial conversation may alienate if not done properly
- Find out what patient/family knows about the medication
- Be honest about acne severity and treatment options
- May be uphill battle
- Patient/Family needs to be comfortable with treatment option
- Usually will be able to tell if patient/family are interested

Optimizing Acne Treatment
- Ask patient:
  - What percentage of clearance is needed to consider treatment a success?
  - If answer is 70 – 100% and patient has moderate to severe acne:
    - Extremely difficult to achieve without Isotretinoin
    - Step wise acne treatment can achieve 50 – 70%
  - Manage expectations

Managing Expectations
What Isotretinoin CAN do
- Eliminate active acne lesions
- Prevent future scarring
- Prolonged clearance of skin
What Isotretinoin CAN’T do
- Fix previous scarring
- Permanently prevent acne
  - Although in 80% of patients acne virtually eliminated
  - Wait 6 months before cosmetic treatments

Managing Expectations
What Isotretinoin CAN do
- Eliminate active acne lesions
- Prevent future scarring
- Prolonged clearance of skin
What Isotretinoin CAN’T do
- Fix previous scarring
- Permanently prevent acne
  - Although in 80% of patients acne virtually eliminated
  - Wait 6 months before cosmetic treatments

Other possible Side Effects
- Temporary hair thinning (10%)
- Rash (7%)
- Intestinal symptoms (5%)
- Urinary symptoms (5%)
- Headache (5%)
- Increased sensitivity to sun (5%)
- Decreased night vision (<1%)
- Depression, thoughts of suicide (<1%)

What to expect
- Dry skin (80%)
- Cracked lips (90%)
- Dry/bleeding nose (80%)
- Dry/watery eyes (40%)
- Muscle/joint fatigue (15 – 20%)
- Headache (5%)
Rare But Potentially Severe Side Effects

- **Bone effects**
  - Theoretically retinoids inhibit bone formation -> risk of fracture or hyperostosis
  - Human trials -> possible demineralization but reversible
  - 1 single case of premature epiphyseal closure ever reported during acne therapy
  - Hyperostosis (overgrowth of bone)
    - Seen in long term therapy (not acne therapy)

- **Mood disorders**
  - Anecdotal and one study with N = 28
  - Changes in brain metabolism in orbitofrontal cortex
    - May mediate depressive symptoms
  - Severe acne more likely to have mental health issues (N = 3775)
  - Severe acne 1.8x more likely to have suicidal ideation
  - AAP position
    - Recommend ongoing vigilance
    - Data reassuring

- **Inflammatory Bowel Disease**
  - Conflicting data
  - If connection exists, small subset of patients
  - More likely to be Ulcerative Colitis
  - Age of onset of IBD overlaps common treatment ages
  - Majority on extended abx therapy before
    - Increased risk for IBD
    - Needs further research
    - Monitor s/s

- **Mood disorders**
  - Anecdotal and one study with N = 28
  - Changes in brain metabolism in orbitofrontal cortex
    - May mediate depressive symptoms
  - Severe acne more likely to have mental health issues (N = 3775)
  - Severe acne 1.8x more likely to have suicidal ideation
  - AAP position
    - Recommend ongoing vigilance
    - Data reassuring

- **Birth defects**
  - Teratogenic
  - Black box Category X
  - FDA adverse event reporting system
    - 6740 pregnancies 1997 – 2017
      - Most SAB/TAB
    - 28% live births with craniofacial/CNS/cardio abnormalities
  - 2006 introduction of iPledge system
    - 4647 pregnancies
    - Mean patient age 24.6 years
    - Stable rates since 2011
    - 218 to 310 pregnancies/year

- **Abstinence**
  - Patients can choose Abstinence
    - NOT preferred option
  - Assess at every visit WITHOUT parent
  - Second form of BC must be “none”
    - Must be confident that patient is not sexually active
  - iPledge workbook for patients has section on Contraception
  - iPledge prescribing information provides Contraceptive guidance
That kind of sounds scary! Why should we use it?

How do I learn to prescribe?
- Find someone who already prescribes
- Dermatology or primary care
- Carefully read and review the prescriber and patient educational kits
- Order materials from iPledge
- Helpful DVD on how to prescribe

Dosing
- First month
  - 0.5 mg/kg/day
  - Starting at half dose reduces initial acne flare
  - Take with food, fats help absorb (except Absorica)
- Second month – Ongoing
  - 1 mg/kg/day
  - Two divided doses
  - Goal of treatment is 120 to 150 mg/kg

Example
- 180 pound patient (81 kg) = 40 mg BID (80 mg day total) with goal of 9618 - 12272 mg
  - First month (0.5 mg/kg) = 1227 mg total (81 kg x 40 mg x 30 days)
  - Ongoing (1 mg/kg) = 81 kg x 80 mg x 30 days = 2430 mg/month
  - Will take about 6 months to reach goal (13,377 mg)

Initial Acne Flares
- Counsel patients that it is not “getting worse before it gets better”
- Initial acne flares are not therapeutic
- Start with lower initial dose
- Can use Prednisone if needed
- Topicals that are not drying (ie Clindamycin) can be continued
- Spironolactone and OCPs as well

Types of Isotretinoin
- Accutane went off the market in 2009
- Available brands – “Branded Generics”
  - Claravis (10mg, 20mg, 30mg, 40mg)
  - Amnesteem (10mg, 20mg, 40mg)
  - Myorisan (10mg, 20mg, 40mg)
  - Zenatane (10mg, 20mg, 40mg)
  - Absorica (10mg, 20mg, 25mg, 30mg, 35mg, 40mg)
- Around $200 to 300/month cash price
- They are substitutable
- Write for Isotretinoin
- Zentane and Absorica have mail specialty pharmacies
- Zentane has patient assistance program
Insurance Coverage
- Most times will need to show step wise approach
  - 3 months minimum
- Can write for generic to avoid brand denials
- Depending on insurance may require MD
- Likely will need a PA/TAR/pre-auth
- May need to PAs, first for 0.5 mg/kg and second for 1 mg/kg

What if I reach the goal and they still have acne?
- Counsel patient that sometimes second course is needed
- Will likely still have some pimples but overall decrease
- If cumulative dose is achieved (120 - 150 mg/kg)
  - Increases likelihood of prolonged/permanent cure
  - 20 - 30% change of regression
- If acne returns trial stepwise approach
  - Topicals -> oral antibiotics -> isotretinoin

Lab Testing
- Baseline
  - Liver function
  - AST/ALT
  - Lipid panel
  - CBC
  - CPK if desired
- Baseline, 1 month, then every visit
  - HCG (if female with reproductive potential)
  - At least once during treatment
  - Liver function
  - Lipids
  - CBC
  - CPK if desired

Precautions
- Cannot donate blood during and for one month after tx
- No extra vitamin A (no multivitamins)
  - Toxicity risk
- No alcohol consumption
  - May potentiate elevated triglycerides
- Pediatric patients
  - Increased triglycerides (25%) – back to normal after stopping
  - Back pain (29%)
  - Drink with full glass of water
  - Take with meal (fat increases absorption)

How iPledge Works
- Computer based risk management program
- Designed to prevent birth defects with Isotretinoin
- Cannot rx Isotretinoin in US without registering
- Pharmacy cannot dispense rx unless patient registered and criteria met
- Patient must have office visit every 30 days
  - Cannot rx without office visit
Sign up with iPledge

Register your patient

Manage Patient

Provider Responsibility - Females who CAN become pregnant

- First Office Visit/Before Treatment
  - Verify qualification criteria
  - Plan for office visits every month with counseling/pregnancy test
  - Educate regarding isotretinoin
  - Obtain consent form (see iPledge packet)
  - Obtain pregnancy test
  - Register patient with iPledge system
  - Counsel on contraception
    - Patient needs 2 forms of contraception

- First Prescription/Second Office Visit
  - 30 day waiting period from first office visit to ensure no pregnancy
  - Repeat pregnancy test
  - Confirm patient counseling in iPledge
  - Enter HCG results
  - Enter 2 forms of birth control patient is using in iPledge system within 7 day window
  - Prescribe 30 days of medication

Register your patient

- Pick if can get pregnant/cannot get pregnant
- If can get pregnant, enter HCG result
- Enter patient demographics
  - Make sure to have last 4 of SSN
- If no SSN, you will need to call the iPledge hotline to obtain a unique identifier
  - Reduces duplicates in system

Confirm Patient Counseling

Provider Responsibility - Females who CAN become pregnant

- First Office Visit/Before Treatment
  - Verify qualification criteria
  - Plan for office visits every month with counseling/pregnancy test
  - Educate regarding isotretinoin
  - Obtain consent form (see iPledge packet)
  - Obtain pregnancy test
  - Register patient with iPledge system
  - Counsel on contraception
    - Patient needs 2 forms of contraception

- First Prescription/Second Office Visit
  - 30 day waiting period from first office visit to ensure no pregnancy
  - Repeat pregnancy test
  - Confirm patient counseling in iPledge
  - Enter HCG results
  - Enter 2 forms of birth control patient is using in iPledge system within 7 day window
  - Prescribe 30 days of medication

Manage Patient

Confirm Patient Counseling

Provider Responsibility - Females who CAN become pregnant

- First Office Visit/Before Treatment
  - Verify qualification criteria
  - Plan for office visits every month with counseling/pregnancy test
  - Educate regarding isotretinoin
  - Obtain consent form (see iPledge packet)
  - Obtain pregnancy test
  - Register patient with iPledge system
  - Counsel on contraception
    - Patient needs 2 forms of contraception

- First Prescription/Second Office Visit
  - 30 day waiting period from first office visit to ensure no pregnancy
  - Repeat pregnancy test
  - Confirm patient counseling in iPledge
  - Enter HCG results
  - Enter 2 forms of birth control patient is using in iPledge system within 7 day window
  - Prescribe 30 days of medication
Checking Patient Status

Provider Responsibility - Females who CAN become pregnant
- Ongoing
  - Counsel patient on adherence
  - HCG in office
  - Confirm counseling in iPledge
  - Enter HCG results
  - Enter 2 forms of birth control patient is using in iPledge system within 7 day window
  - Prescribe 30 days of medication

- Last dose
  - Same as ongoing
  - HCG in office and enter results
  - Confirm counseling
  - Enter 2 forms of birth control patient is using in iPledge system

Provider Responsibility - Females who CAN become pregnant
- One month after last dose
  - HCG in office
  - Enter HCG results
    - If no final HCG is entered -> Lost to Follow up -> you/patient may be contacted
  - Birth control 30 days past last dose
  - Do not give blood for 30 days after last dose

Entering HCG Results

Patient Responsibility - Females of Reproductive Potential
- Log in to iPledge system during/after office visit
  - Within 7 days of visit
  - Complete patient counseling
  - Identify the 2 forms of birth control patient is taking
- If incorrect answers x 2
  - Review materials and try again
  - Email to prescriber with alert of incorrect information
A Review and Case Study

Case Study

- JW, 16 years old, tried and failed several treatments over 6 months. Desires to start Isotretinoin. She was seen 30 days ago and had a negative HCG in clinic, signed the consent forms, and started on Depo injections. She is here today for her follow up visit. Per patient she received her log in information for iPledge and was able to log in successfully.

What are some of the things we should counsel patients on before starting Isotretinoin?

- Chapped lips and dry skin are almost guaranteed to occur
- 20% of patients may have bone/joint pain
- Depression/suicidality are extremely rare but should be monitored
- Acne may reoccur after treatment
- All of the above

What must be done at today’s second visit?

1. Repeat HCG, Labs, confirming patient counseling in iPledge, send rx
2. Repeat HCG, Labs, send rx
3. Since patient had negative HCG/started Depo, send rx
4. Confirming patient counseling in iPledge, Repeat HCG, send rx
Dosing
• Patient weighs 160 lbs at today's visit
• Initial dose will be 36 mg qd
  • 160 lbs = 72 kg. Initial dose is 0.5 mg/kg = 36 mg. Divided in 2 doses = 15 mg
  • No 15mg option so 10mg in am and 20mg in PM
• Next month will increase to full 1 mg/kg/day
  • 30mg BID

What is her goal mg/kg?
• 7272mg – 8640mg (100 – 120 mg/kg)
• 8725mg – 10909mg (120 – 150 mg/kg)
• 10800mg – 12240mg (150 – 170 mg/kg)
• Too early to tell, need to assess response

It’s 2 months in to treatment. What do we need to do?
• Repeat Labs
• Assess for response
• Assess for patient satisfaction
• All of the above

What do we need to do at the last visit?
1. Register negative HCG in iPledge
2. Counsel not to donate blood x 6 months
3. Continue taking birth control for at least one more month
4. Both 1 and 3

We’re at the end!
• JW completed 6 months of therapy and ended with 11880 mg total which is 165 mg/kg
• She needs HCGs at last visit and one month after completing treatment
• She should not donate blood for one month

Patient returns 6 months later and has reappearance of acne. What should we do?
• Another round of Isotretinoin until clear
• Counsel acne will likely go away on it’s own
• Monitor and follow up in another few months
• Depends on severity
Prescribing Tips and Tricks

• There is a lot of misinformation on the internet
• Review Isotretinoin Fact Sheet from iPledge
• Reiterate that you are here to help answer questions/concerns
• Aim for 150 mg/kg in total
• Results in increased clearance
• Some literature up to 220 mg/kg for longer remission
• Schedule Females who can reproduce visits for 35 days apart
• Accounts for 30 day rx window and weekends
• Sunscreen, Vaseline are essential
• Practice iPledge yourself before delegating MAs

References

5. Hitzeman, N. Family physicians are well suited to prescribe Isotretinoin. Am Fam Physician. 2016;94(5):342‐344