A randomized controlled trial investigating the pediatric patient experience of subantimicrobial dose doxycycline for acne treatment

- Study protocol
- Statistical analysis plan
- Informed consent form

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Study Protocol

Inclusion criteria

Participants are eligible for inclusion in the study if they: are between ages 13 and 17, diagnosed with moderate to severe acne, did not have other skin conditions on their face, were not previously treated with antibiotics for acne nor received antibiotics for any reason within the last month, did not start a new prescription regimen for their acne within the last three months, did not obtain a positive pregnancy test in the clinic, and had no cognitive impairments. This minimizes confounding factors in treatment response and evaluation of acne (e.g., erythema from other skin conditions). 22 adolescents were identified as eligible and, with their parents, consented to participate in the study during the 11/20/2020 through 09/20/2021 study period. No changes to eligibility were made during the study period.

Randomization and Blinding

Once consent is obtained, eligible sample adolescents are randomized in a non-blinded, parallel fashion and in equal allocation to take either 20 mg or 100 mg doxycycline BID for 12 weeks. Additionally, the same over the counter regimen of Adapalene 0.1% gel and Benzoyl Peroxide 2-5% wash was prescribed.

Patients are randomized by choosing a folded piece of paper from a bag that determined their dose. No blinding to treatment arms occurred to mimic a real world where patients are informed of their dose. This allowed for the determination of patient-perceived effectiveness despite patient awareness of taking a lower dose.

Materials and methods

Participants are emailed a brief Qualtrics survey[18] link on the day of enrollment and every two weeks thereafter to self-report their doxycycline dose and perceived facial acne severity using the validated *Patient-Centered Acne Severity Scale*[19] containing a 10-point visual analog Likert-type scale. Each respondent is also invited to report any medication changes and submit open-ended comments concerning their use of doxycycline or their acne experiences. Those who submit at least three survey responses will be included in the analysis. After 12 weeks of treatment, participants complete a follow-up appointment at three months for clinical evaluation.

All participants are to be screened, enrolled, and treated through the Messenger Dermatology Clinic. Treatment is initiated at the same visit as enrollment and data collection ends at the three-month appointment. Patients picked up their prescription from the pharmacy of their choosing; the clinic and study personnel do not dispense the medication themselves. The Qualtrics software is programmed with a de-identified study identification number and message encryption.

Statistical Analysis Plan

Data analysis will be performed with *S.P.S.S. Version 28* analytic software using Friedman repeated measures test and Chi square test. For all analytic procedures, a two-tailed coefficient $\alpha < 0.05$ will be observed to indicate statistical significance.

Research Participant Information and Consent Form

You are being asked to participate in a research study and your parent is being asked to provide parental permission. Researchers are required to provide an assent form/parental permission form to inform both of you about the research study, to convey that participation is voluntary, to explain risks and benefits of participation, and to empower you to make an informed decision. You should feel free to ask the researchers any questions you may have. Both of you need to agree for the child's participation in this study.

Study Title: Effectiveness of Sub-Antimicrobial dose of doxycycline in the treatment of acne

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1. PURPOSE OF RESEARCH

- You/your child are being asked to participate in a research study of whether a lower dose of the antibiotic doxycycline is still effective in treating acne.
- You/your child have been selected as a possible participant in this study because we would normally treat this type of acne with doxycycline.
- From this study, the researchers hope to learn whether this lower dose is effective in treating acne.
- You/your child's participation in this study will take about three months, and possibly up to six months.

- An alternative to participating in this study is to receive the standard dosing regimen of doxycycline, which is 100mg twice a day.

2. WHAT YOU WILL DO

- As part of this study, you/your child will be asked to fill out the initial screening document and consent forms. During screening, female participants of reproductive age will be required to take a pregnancy test, as part of standard drug safety processes. The Messenger clinic will cover the cost of this pregnancy test.
- You/your child will be asked to take your prescription as directed. As part of this study, you/your child will be randomly assigned to take either 20mg of doxycycline twice a day or 100mg of doxycycline twice a day.
- You/your child will also be asked to fill out a brief online questionnaire at home every two weeks, in order to evaluate whether or not you feel there any improvements in your acne.
- Lastly, it is important that you/your child come back for a follow-up appointment after about three months of treatment for clinical evaluation.

3. POTENTIAL BENEFITS

- You/your child's participation in this study may help us understand how to best treat acne while decreasing antibiotic resistance. Antibiotic resistance is when bacteria are not as easily treated by antibiotics. Widespread use of standard dose antibiotics can make bacteria resistant and lead to infections that are more difficult to treat in

the future. The lower dose of doxycycline in this study is too low to affect bacteria, but still has anti-inflammatory action.

4. POTENTIAL RISKS

- It is possible that you/your child may have an adverse reaction to the antibiotic doxycycline. Common adverse reactions to include nausea, vomiting, diarrhea, and a rash in response to sunlight exposure.
- It is also possible that this lower dose of doxycycline may not be as effective in treating acne as the standard dose, and that you/your child's acne may not improve while participating in this study.
- Doxycycline is contraindicated in pregnancy. If you/your child become pregnant during the study, the drug needs to be stopped immediately due to the risk to the fetus and you/your child will be withdrawn from the study. We encourage females of reproductive age who may become pregnant to take proper precautions to prevent pregnancy.
- Like any medication, doxycycline carries its own risks, described on the package insert. These risks would be present regardless of participation in the study. One such rare risk, as with all antibiotics, is inadvertently causing antibiotic resistance.

5. PRIVACY AND CONFIDENTIALITY

- As a participant in this study, you/your child's privacy and confidentiality will be rigorously protected.
- The data for this project will be kept confidential. You/your child will never be identified in any reporting of the data.
- Information about you/your child will be kept confidential to the maximum extent allowable by law.

- The patient surveys are anonymous surveys through Qualtrics, a secure survey system, with no identifiable data tracking to the submission.
- Once collected, data will be deidentified and stored on a password-protected, secure server until completion of the study. A correlation tool will be used to de-identify data that will be kept separately in password protected files.
- Information that personally identifies you/your child may be removed from the data, so that it may then be used for future research studies. After this de-identification it may be used for future research or distributed to another investigator for future studies without additional informed consent from you/your child.
- Clinically relevant research results will not be returned to you/your child unless you/your child request it.
- The research staff and MSU HRPP are the main entities who will have access to the data for the duration of the study, and for the three years following the completion of the study. The HRPP oversees research studies to ensure patient safety. It is possible that the Food and Drug Administration may inspect the records.

6. YOUR RIGHTS TO PARTICIPATE, SAY NO, OR WITHDRAW

- Participation is voluntary. Refusal to participate will involve no penalty or loss of benefits to which you/your child are otherwise entitled. You may discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled.
- You/your child have the right to say no.
- You/your child may change your mind at any time and withdraw.
- You/your child may choose not to answer specific questions or to stop participating at any time.
- Choosing not to participate or withdrawing from this study will not make any difference in the quality of any services you may receive.
- You/your child will be told of any significant findings that develop during the course of the study that may influence your willingness to continue to participate in the research.

7. COSTS AND COMPENSATION FOR BEING IN THE STUDY

- There will be no additional cost to you/your child for participating in this study. You will be responsible for the normal costs involved in treatment (such as prescription co-pay, etc), but there is no additional cost due to participating in the study.
- You/your child will not receive money or any other form of compensation for participating in this study.

8. INJURY CLAUSE

- If you are injured as a result of your participation in this research project, Michigan State University will assist you in obtaining emergency care, if necessary, for your research related injuries. If you have insurance for medical care, your insurance carrier will be billed in the ordinary manner. As with any medical insurance, any costs that are not covered or are in excess of what are paid by your insurance, including deductibles, will be your responsibility. The University's policy is not to provide financial compensation for lost wages, disability, pain or discomfort, unless required by law to do so. This does not mean that you are giving up any legal rights you may have. You may contact Dr. Gallagher with any questions or to report an injury.

9. CONTACT INFORMATION

If you have concerns or questions about this study, such as scientific issues, how to do any part of it, or to report an injury, please contact the researcher:

Dr. Michelle Gallagher
Messenger Dermatology
1515 Lake Lansing Road, Lansing, MI 48912
Phone: 517-487-0128

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Michigan State University's

Human Research Protection Program at 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at 4000 Collins Rd, Suite 136, Lansing, MI 48910.

10. DOCUMENTATION OF INFORMED CONSENT.

Your signatures below means that you voluntarily give your permission for your child to participate in this research study and that your child has given his/her assent to participate.

_____ _____

Signature Date

_____ _____

Signature of Assenting Child (13-17) Date

You will be given a copy of this form to keep.