Long-term effects of oral antibiotic treatment for moderate to severe acne vulgaris; a scoping review

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Alviingcns läkarhus

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Abstract

Tntroduclion Acne vulgatis isa common dcnnatological conditton affeccing a large propo111on or thc popula l10n. Oral antibiotics are used l'or moderate to scvcrc acne. oftcn lim1ted 10 thrcc months duration. Since acne symptoms vary naturally over t1mt!. c, aluatmg effccts of tht!rapy not only short-ccnn bul ulso maimcnancc is important 10 cletemiinc trcotment outcome.

Aim Jhe aim was 10 imt!stigatc studies on maintt!mmcc cffcct arter ccssat1on of oral antib1ot1cs for moderate 10 severe acne vulgaris, and to summarisc rhc me1hod. uc1hsc;:d.

1\lethod In this scoping rcview, PubMcd and Scopus wa • utihscd in conducting the ,t:a h. lnclusion and e,clusion criterin were set prior, and thc citation-; y1clded wt:rc ,;crt!cncd for eligibility using ʟhese criteria. Data was complic<l 1mo a sprcad shci!t

Result 14 a11iclcs were mcluded, with varymg trc;:ulmcm comparisons mve·t1gutcd and severnl mcthods for grading and <lctcnnining outcomc utili ·e::d. Lcs1on count and c, aluat ing cffect usmg previously gradcd sevt:nty, were predommant techn1qucs. \la111tenam:c cffccts wen.: studied for bctwecn two ,vecks to s1x months. and <liffered marginally whcn comp,1ring dosagc and typcs of oral antibiot1cs. Maintcnancc 1mpn.>\Cd wht.:n usmg topical agent'.'-. as follow-up treatmcnt, and aftcr isotri!tinom.

Il is challt:nging to interprct and summan.le trcatmenl cffccts as th1.: includcd st ud ics d1d not rd) 011 a single gol<l standard for grad ing se::verit) and quant,fymg outcomc Ct11Tenl c, ,dcncc suggesl. oral ,1111,biotics arean effcetivc treatment for acne. although. no dm,cally reh.:vant conclusiorn, can be sum1ised rcgarding thc dun:111011 or cffects or if chh 1-.. hc ʟ prnctice. bo11cttnoin shov.cd impro,ed maintenancc, howc,·er, thc trcatmenl ,.., comphcatcd by a nst.. of scvcrc advcr,c cvcnts.

Conclusion 17,ert: arc fcw studies cvaluating long-tcnn effects arter cessat1on of oral ant1bio1n.:s, a standard isccJ classification of acne and c, nluation or outcome is csscnt ial in order ʟo full) dcte1111111c optimal treatment regimcs.

Table of contents

Introduction

Acne isa skm discase ca11sed by incrcased sebum production (I). d1smption in thc shcddmg of ebaccous follicle epithclium in the ..,kin (lcading lO Lhc fonnation of comcdoncs) and the prcscncc of the bactcria Propio111bac1erium acnes (P. acnes) causmg mflammat,on (2). Acne is sometimcs referred Lo as acne vulgaris. mcaning common acne. Acne vulga1is was 111 20l0, estimatcd as the 8h most prcvalenl diseasc globally, affcctmg ovcr 600 million pcuplc prcdominantly in ages I 0-24 (3). and nearl} cvct)0nc b\!t\\ ccn t he agcs of l5-17 (4). Aene can ha,·e physical consequcnces. such as -.camng 15). as \\Cll as emotmnal, mcluding emot1onal sm:ss. low sclf-csteem and dcpn:ssmn (6).

C'irading the sevcrity of 1cne is oftcn perfom1cd by physiciam \.Vithout a -.;ystcmatic approach. often resultmg 111 subject1ve class,fication. In a maJotity of thc litcrawre acne J'i categ:onscd as mild, moderate and sevt:rc, but 0\'er 25 d iffcrcnr mcthncls or g.ra<ling are uscd globally (7). lfo::se thrcc aforemt:ntioncd degret:s or sc\'crily af\! somctimes catc onscd bast:d on number of comcdoncs, number of intlmnmatory Jcs,ons. total lcsion count or prcscnce of C}'its (7). One commonly uscd mt::Lhod is thc Lceds Rc,1scd Acne (im<l ing System (8). based on thc Lccds technique dcscribed by Rurkc er al. (9) in 19!<-t "hcn: a !arge photogrnphtc databasc is useJ for comparison, ba-.;c<l on c:-.tcnt of inflammation. range and s11c of intlanu11atory le. ions, and ,r ct)lhcma 1s pn:!scnl

Ocpcnding on thc scvent\ or acne, differt:nt trcatmcnt methods arc uscd. C'urrenl S" cd1sh gu1delines prov,dc recommcndations for tn:atmcnt of acne (I 0). l11c comer,;tonc ,._ rop1cal Lreahncnt. both as monorhcrapy and in combination with oral 1n:a1mcnt options. The first line topical trcatments for mild acne are adapalcne, hen1o>l-perox1<lc and azela1c ac1<l In moderate acne a combination of adapalenc and bcnzoyl-pcrnx1de is uscd. or ·econdly, bcnzoyl-pt::roxi<lc and topical clindamycin. In moderate acne" hcn topical trealmcnt has pro, en in ·uflici nt, orm ·evt!n.: fonns of acne. oral trcatmcnt w11h amibiot1c • can be admintstcrcd fora limitcJ period or Lime. as n rnmplcmcn1 lo top1cal trcarment. O1ffcrcnt fo1ms of ldracyclmcs ,tre mosl commonly 11..;cJ. <luc 10 thcir lipid-solublc nalllre and abllity to pcnctr.itc mlo lhc comcdoncs. and is

1he recommcndc<l Lrealment in Swcdcn toc.iay (I 0). All oral antibiotic fonm havc proven mon: cffeclive than placebo, with most evideucc present for tetracyclinc (11), alLhough no single agent has proven comparativdy supcrinr (12). Ilowcvcr. an im.:rem,ed risk of dcvcloping res1stant P. acnes against c1ythromycin ha-; hccn <.kmonsLrnled (I I). lhcrc 1s no const:nsus among specialist regard ing dosage (1.1) and Lud,c, have shown small differenccs in Josc-<lependent cffccts (12). Two ro chrcl' months of trcatml'nl is often rcquircd LO ohtain clinical cffcct and no addition,1I 1mprovcmcnt is :,;cen ,vith longcr duralion (12, 13). Prcscription pnttcrns diffcr globally and a11Lih101ics arc ofrcn prcscribed for long periods of Lime. lu a systcmaLic rencw by \\'alsh ct al. (1-t) a mean d uration for antibiotics usc of 129 days was sho,\ n. When oral am1ht0Lics are concludcd. a topical agent, such as adapalene or bcnzoyl-peroxide, 1s rccommcndcd as munolhcrapy to obrnin prolonged effcct and dccrease thc nsk of rdapsc (15).

Or.1I ad ministrarion of ant ibiotics has hccn proven to incrcasc Lht: lcvels of rcsislanl bactcria in gut flora in both acne patients and rhcir retat ives (16). Srud ies ind icatc nn 111creascd cutancou'i cokrnizarion wich P acnes :ifrer rrcatmcnt with oral a11tibioL1cs. nlthough contamination „·1th rcsistant P. acnes has rmher been suggcstcd as ong111at111g from person-to-pcrson spr1.:ad hl!l\.veen acne patients and orhcrs rcgard less of oral trcatmcnt (17). TI1c presl!nce of rcsisLant P. acnl!s has becn dcmonstrnled a • clmically rclc,·anl. rC!>ulting 111 reduccd rcsponsc Lo treatmcnr and increased risk of rclapsc. bu1 as to hcnv nnd to what degrl!e therc is no clcarevi<lence (17). Topical antibactcnal agents havc bccn associaLed witb an incrca.'il!d risk of rl!sistanl bacLeria on thc skrn (18, 19) To dccrcase Lhe risk of rcsistancc while using topical a11tibi0Lics, bcnzoyl-perox1d e 01 a toprcal rctinoid 1s rccommcn<lcd in combinntion (14. 17).

ln Swcdish guiddines, a limiL of Lwo courses of antibiotics per lifetimc has bccn impk111enled in an attcmpt to <lecrease antibiotics use and resistancc (I0). Prt!viously rccumng courscs of antibiotics have bccn common prncticc, somc studies ·uggc:,ling a mcan Or four courscs per paLienl prescribcd over five years (20). I Γornl antibiotic in comhination with topical treatment gives insufficient effect, oral isotr tinoin can be cnn.;idered (10). lsoln.:tmnin isa systcmic rcLinoid and is thc mosl d'fecLive trentmcnl

for acne. Mobacken el al. (21) cstimatcd 80-85% of pa1ients 1reu1ed w1th 1sotrctinom \'ven: l"n.!c from acne after four to six months of trcatment and les· than 30% rclapsc. Adverse effecls ol' thc trcarmcnt are, on the 01her hand. many with depressi on leading. lo suicidc and tcratogenicny being ·ome of' thc most scrious (22).

Dm: 10 Lhe paucity of c, idence regarding dosage, typc of antib1otic:, nncldurntion of rhcrapy. the effect of oral antibiotics against acne ha!> bccn qucstioned. refening In lhc strong placebo effecl in thi pa11icular disease and the fact that acne oftcn improves spontam.:ou ly wirh age (23). The risk or rccun·cncc of acne symptom arter ccssat1on of thl!rapy havc bccn studied mostly for isotretinoin (24), and data conccrning long.-h!rm effrct aftcr trcatmcm ,, ith oral antibiotics arc. carcc. Antibiotics resistancc 1s a gro\\ mg issue in socicty today and decrcasing the use of antibiotics isa priority in healthcan.: scttings all over thc workl. Considcring the i·sues wilh high prcvalcncc of acne and mcrcasing res1stance againsl antibiotics. it is imponant to evaluatc our cuncnt treatment rccormnemlations. Oral antibiotics are prescrib(:tl for11umcrous and prolongcd cou1--;cs globally, includmg in Swedi ·h primary hcalth care. ofte;:n resulting m msufficicnt effect. mcrea ing antibiotic rcsi!>tance and rel"t!mlls to dcrmatolog1sts for isotretin<>m trcatmcnt.

The aim of this study was to review cvidcncc rcgard ing long-tt!m1effccl aftcr ccssat1on of oral antibiotics on acne symptoms in an a11cmpt to clarify whether current recommendations area susrainablc option both rclating to trcarmcm cfficacy and antibioti<.: rt:Sistancc. Sincc acne isa dise;:ase in which symptoms change naturalt, mer timc and many factors contributc to thc varying degree of severity, it is impo11ant not only to study the direct effects or thc treatmcnts. bttt also the long-tl!rnl cffccts aftcr 1rcatrncnt has bccn concluded.

Aim

l11c rum of this study wa lo invcstigatc to which degree the effocts of ornl antibiorics for acne at'ter cessation or thcrapy rclating to recum!nce or worsening of acne symptoms has been studiec.l. An additional aim was to campare methodology i11 order ro evaluate comparability of the studies, rcgarding method of classifying acne. mcthod for

I:\aluaLing Lrt!atmenl outcomc, lypes of ornl antib1otics mvcstigatcd, length of folio\\ -up arter concludcd amibactcrial thernpy, and lrcatmcnt cffccL .

Mcthods

Study design

ll11s stu<ly was set up as a scoping rcvicw according to the framcwork crcate<l hy Arksey and o· tallcy (25) lo investig:ite the aforcmc111ionecl postulated quc tion. :'-Jo attcmpts wcrc made LO assess risk of bia!. or qualiLy of the includcd srud ics <lue to th stu<ly c.lt:'>ign. '-Jn quanllfication of cffccts \Vas attempted.

Litcrature earch

11,e searcb \Vas conductcd in two electronit: databascs. PubMcd and Scopus, on thc 25[1] of l\larch 2024. The search que1y cons1stcd of lC1ms regard ing acne vulgaris, <lcgree of se\erity, aclrnm1strnt1on of trcatmcnL, antihiolics. and long-tcrm cffccts. TI1e search string wm, tailorcd 10 thc spccific requirements of the two clcctronic databases:

- PubY1ed: (acne) AND (moderate OR scvcrc) AND (oral OR per os) AND (anti-bactcrial agents OR antibiotics) Al\O (lrcatmcnL outeomc OR Lime ractors OR follow-up OR long-tem1).
- Scopus: acne A D (moderate OR severe) AND (oral OR "pl!r os") A\JI) (antibiotics OR "anLi-hacterial agents") AND ("tn:aLmt!nl outcomc" OR "Lime factors" OR "follow-up" OR "long-tt:nn")

Potent ially relevant c1tatmns werc screened using predctcnnincd inclusion and cxclus1on critcna. 11,c citaLions were scrcened for rclcvance, fir·t from tirlc, thcn abstract, an<l finally precured in full-text for asscssmcnt of eligibility.

Inclusion criLeria were as follows:

- PaLients with moderate to scvere acne vulgaris
- Usc of oral amibiotics
- Follow-up afler cessation of thcrapy with ornl antib1ot1cs

- Imcstigatcd outcome includ ing degrcc of acne symptoms, severily of the disea. c, and/or recurrence of symptoms

Exclusion cnte1in included:

- Editorial reviews
- Studies only rcporting discontinualion duc to advcrse events
- Comparison with other trcatments not recommended in guidclincs or not uscd in clinical practice, such as dtctaiy supplemt!nl-.., photodynamic light thcrapy. peding, spironolactonc and non-stcro1dal anti-inflammatory drugs. Compari·<m w1th oral cuntrnccptives were also exduded.

o limitauons were mad regarding type of comparisons, such as placebo, topical tn.:almcnt or isotrcti.noin. to gel the broadcst possible scope of cum:nl l!Vidcncc. Similarly, no !imitation was set for year of pubhcation, to include all historie studies that gmdt:lines are based on today.

Data ynthe i

Data from tht! includcd a1ticlcs was colleclecl and compilcd in a spreadsheeLU'-tng E,cel. 111cluding the following: ycar of publication, country, study design, srudy pop11lat1on, dcl'inil1on of acne severily, typt!s of trcatmcnt and potential comparisons madc, length of 1realmcrll. follow-up duration, outcome and rncthod of quanLification.

Ethics

Mo t or thc mcluded studie· rt!po11cd crhical approval and wrilll.!11 conscnt from patients, or thcir legal gunrdian. but not all. TI1is information was lacking for onc a1t1clc publishcd in 1978, and fora fcw pubtishcd in less renowncd joumals. Ethical approval wns not set as an inclu!-.ion critcrion duc to not wanting to limit Lhc scopc of find mg-.. althoug.h thc rcliabtlity 01·thcir rcsults and cthics in obtainmg thcn1 could be qut: tioned.

\cm: 1s a disease with ft!w serious hcalth risks. apart from scarring and psychological 1111phcal1011s. Some of the thernpies an: associatcd wirh graver risks. -.uch as sUtc1de or

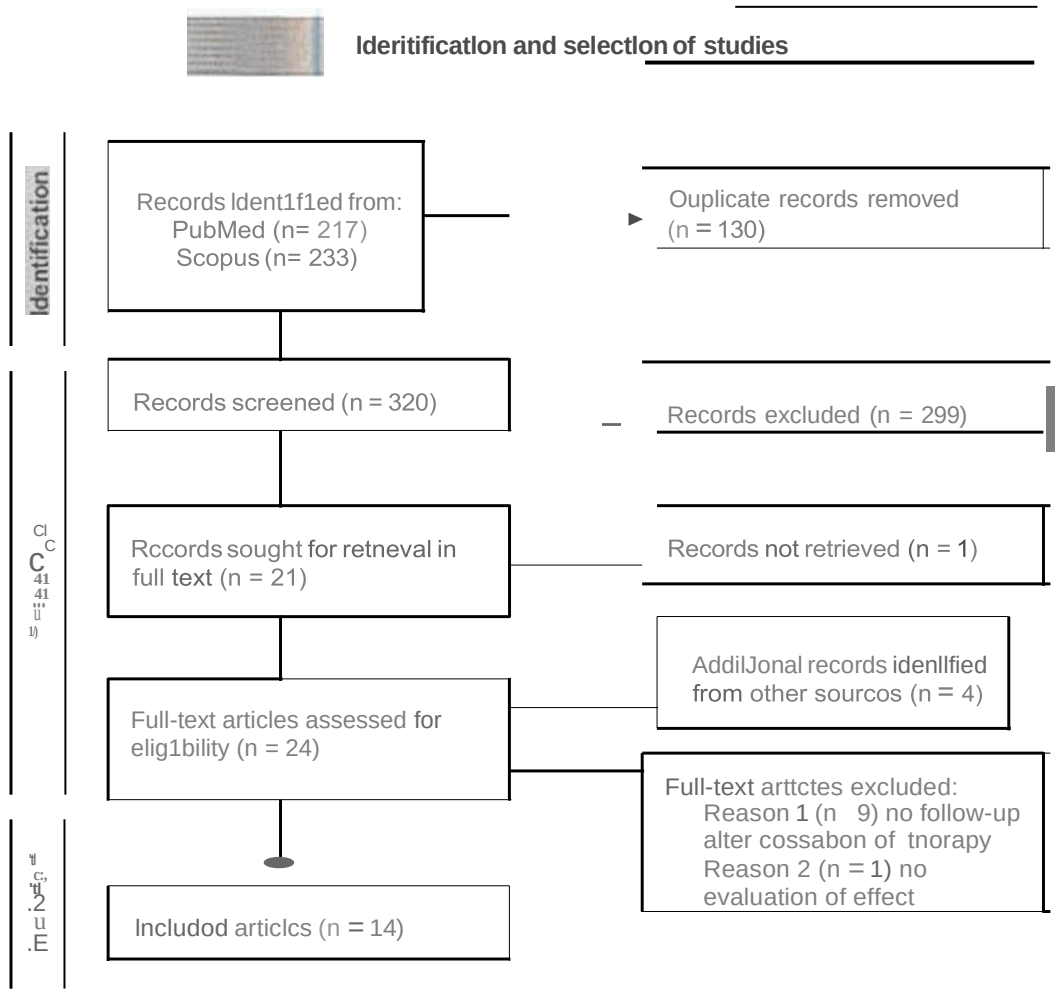
tcratogen1city for isotrctmom. and considcrations regarding both risk and bcncfit of rreatment has to be madc. Oral antibiotics are associated with risk of rcsistant bactcna. and can thercforc bl: con«-idered a global threat. Due to tlus study bcing a scoping re,1ew ha·ed on previous studics no cthical approval was attained, howevcr. a systcmat1c approach \\as utiliscd in collecting data in order to improvc rcliability.

Results

Literature Se}1rch

The ongi nal search y1cldcd 2 I 7 citations rrom PubMed and 233 from Scopus. 450 in total. Aftcr rcmoving duplicates. 320 citations rcmaincd. After screening for relenmce. lin,1 ba:-.ed on title and then abstrnct, 299 studies werc excluded, r..:sulting in 21 bci11g :-.ought for retrieval in full text. Onc study could not be acquired.

20 studies werc prncured, read in full and asscsscd for eligibility. From refcn!ncc5. an add1t1onal fourswd1cs \,crcide11Lified as relevant to thcaimand wcrc included in the c,aluat1011.)'leldmg 24 aniclcs asscsscd for cligibility. Nine were excludcd duc to not mclud ing any follo\\Alp aftcr cessat ion of therapy. One study only invcstigated riskor mfoction Sl.!comJal)[1] Lo trt!atment with oral antibiotics and did not cvaluate effecc and \\.a:,. thcrefore ex<.:luded. This resultcd in 14 a11iclcs bcing included in this swdy, chc sdcct 100 can be stud icd in full in Figurc I.



Figurc **l.** Flowchart of sludy ·election proce·s

Study charactcristics

Characteri:.,;tics of the included articles are summarised in Table I. Yean:, of publication rang d bctwccn 1978 lo 2020, and 26 to 253 patients wcrc mcludcd. The majoril) wcrc ra11domiLcd conlrollcd trials (RCT), although coho11 studies wcrc also includcd, both 1.:ltni1.:al reports. pilot and non-comparntive studies. 171e severity of acne was modemte aud or SC\Crc. In onc study (26), no specific scvcrily was set m, an inclusion cntcnon. hm\t!\t:r, grading was perfonm:d and defimtion presentt!d. thus meeting the inclu,ion c1itena.

Table l. Charactcris11cs of mcllldcd c;tt1d1es

Authors	Year of publicat ion	Country	Type of study	Blinded	Population (n)	Definition of severity	Acne severity included
Alirezai el al. (27)	2007	19 cenlre in differcnt countries in Europc	RCT	lnve lig ator-blindcd	136	ee<1s revised acne grad ing sy!)ll:Jll	Moderate to modcrntc-scvcre
Babaeinejad et al. (28}	201 I	Tran	RCT	Doublc-blindcd	100	CCAC*	Moderate
Ferahbas et al. (26)	2004	Turkey	RCT. Cross-over trial	Doublc-blindcd	46	Lccds rcviscd acne grnding sysrem	
Gollnick et al. (29)	2001	Gennany, Austria. Swit7erland	RCT	open-label	85 (only males included)	Leeds grading scale	Scvcrc inflammatory, nodular, Lecds 4
Gould et al. (30)	1978	Cl<	Cohort study	no	57	Subjcctivc mod ificd scalc (0-10)	Moderate
Hasibur ct al. (31)	2013	Bangladesh	Coho1i study	opcn-label	82 (only adolescent incl uded)	-	Moderate to severe
Hayashi et al. (32)	2011	Japan	RCT	open-label	150	Jnpanese acne study group criteria	vfodt.!rate lo severe
Ilayashi et al. (33)	2012	Japan	RCT	open-label	149	Jnpanese acne stucly group criteria	:\fodt.!rate lo scvcre
Kircik et a 1. (34)	2016	USA	Coh01t study	open-label	32	IGA**	\foderate lo scvcrl!, IGA 3-4
Oprica et al. (35)	2007	Swcdcn	RCT	110	52	Lccds grad ing scale	\fodernte to severe, Leeds >3

Tablc I. C"haracle1isLics of induded studies *(co11ti11ut>d)*

Poulin tt al. (36)	2011	Crulada, USA, rrancc. Pucno Rico	RCT	Doublc-blindcd	243	[GA**		Sevcre, lGA 4
Rchman rt al. (37)	2020	LK, Malaysia	RCT	lnvcstigator-blindcd	26	GAGS**"'		Moderate
Tan CI al. (15)	2012	USA, Canada	RCT	J)oublc-blinded	243	lGA**		Severe, IGA **4**
Thiboutot ct al. (38)	2006	USA	RCT	lnvestigator-blinded	253	-		Scvcrc

,i.Conscnsus confcrcncc of acne classification

**rnvcstigatol's global asscssmcnt

*** Global acne grading system

lcthodology of thc includcd studies

In Table 2, a summary or meLho<lology of Lhc includcd scudies is presentcd.

ethods for grading and evaluating effect

\,fan) differcm \\.U)S or quantifying cffcct \\ crc utiliscd, and in scvcral of thcsc stuJ1cs a rigorous evaluat1011 wa<; perfom1ed u<;ing multiple met huds. Lesion counL '" as Lhc mosl w,cd Lcchniquc. whcrc thc numbcr of lcsions werc countcd cithcr on thc facc, chcst anti·or back, or 111 a segment of thc facc. 111c lesions wcre often acldditionally cl1viclcd 1nto ubtypes, uch as non-infla1t1111alo1y or comcdoncs, inflammato1y, and cysts. The ks1on-; \\ crc coumcd at cvcry follow-up and compared with ba·eline, and rl!ported t!tthl!r a:-. a decreasc in absolute number of lcsions or in pcrccntagc.

Anothcr mcthod wa..., using definition or scvcrity in order to quantify cffcct. cvaluacmg irnpro,·ement of the previously classificd tlcgrcc of symptoms. Lccds grad ing. scalc. or thc updatcd version, Lccds rcviscd ,icne grading system, is one or Lhc mcthods ror das:-.il'ying acne se\'erily u:-.ed in se\'cral of thc includcd studies. I nvcstigators global asscssmcnt of acne SC\'cnty (fGA) wa • another utilised scale, in ,vhich ·everi1y i· grad\!d bt!tween 0-5 based on typcs of lesions and proportion of thc focc involvcd Conscnsu<; Confcrencc on Acne Classification (CC/\C) wa. u.cd in onc study (28). and a11ulhcr (37) utiliscd Global acne grnding system (GAGS) Lo <lefine severity. .lapant!se Jrne ,;tudy group criccria was uscd in thc two studies from Japan (32, 33). based on mllammarory lcsion count per half face. Gould et al. (30) utilised a. uhjecti, c mod ıfied cale of severity 111nging from 0-10 bascd on invcstigators grad ing. Two studies (31. 8) d1d not clearly describe Lheir definition for classifying acne, and includcd symptom ·cventy was simply ref'em <lLO as moderate or sevcrc.

Thl: classil'icatiun:-. of scvcriry wcrc ut1liscd at basclinc and duri.ng follow-up 10 detc:m11111! impmvemenL.for examplc percc magc imprO\ cmcnt of I*GJ*\. or companng median acn\!scorn base<l the Lec<l. grn<ling scalc bctwccn visits.

In :-.ome or the stu<l1cs, altcmpts wcrc madc ro synthctisc thcir own mcthods of c\'aluating cffcct. Onc cxamplc was maimcnancc succcss ratc, which was uscd in chrcc

studies (27. 36, 38) with similar definitions, base<l on percenLage of subjects""ho mamtained at least 50% improvement in tenns of percent reduction of lcsions at follow-up comparcd to basclinc. Poulin ct al. (36) additionally used the tenn IGA maintenance success rate. pcrccntagc of subjccts with thc same or bcttcr IGA scorc comparcd w1th ba:,dinc. Thiboutot cl al. (38) uscd an inversc measure. failure mte, calculate<l as I00% minus maintcnance ratc.

In a 1"1.:v, stutl,cs, **P.** acne.., count was analyse<l. either with pholo analysis (36), from skin samples (35), or bactennl examination tests taken from lcsions (32). From skm samples and bactcrial Lests, a determination of presencc of resistant sLrnins and cak:ulaLion or Ml(' (minimum inhibitory concentration) was perfonned. 11lis testing was by *1* layashi el al. {32) only conducted at baseline and cnd of trcatmcnr wirh ant1biotics. whcrcas 1hc othcrs mcludcd add itional tests after thc maintc11ancc period.

Othcr morc general methoc.h of evaluating effecL were investigator and patient global assessment of therapeuttc result and globalseverity assessment, the mcthodology of which is noL <l scribed in further detail. Severulstudit!S use<l questionnuires for patients regardmg treatment satisfaction or self-assessed improvement. Tan et al. (15) ut1hsed a que·tionnaire for invesrigators at the cnd of follow-up, in\'cstigating thcir imenrion of prcscnption going forward.

Tablc 2. Rl!suhs regarding 1111;!lhodnlogy or thl.! incluttktl studil!..,

Authors	Oral antibiotics	Topical agents during oral treatment	Comparison	Duration of oral antibiotics	Follow-up time	Topical agents	Method of evaluating effect
Alire .ai et al. (27)	Lymecyc:lim:	/\dapaknc Vchiclc	Topical trcntmcnt tlunng follow-up	12 wccks	, 12 wccks	t\dapalcnc Vchiclc	Maintcnancc succcss ratc, les,on count, global st!\erity asscssmcnt
Babacincjad ct al. (28)	Doxycyclinc Azithromycin (pulsed)	no	Do:-..ycyclinc vs Azithromycin	3 months	3 rmonths	no	Lcsion count (incl subtypes). Michaclsons acne severitycorc
Ferahbas et al.{26)	Roxithromyci 11		Roxithmmycin vs placebo	4 weeks	2. 8 wceks	no	\,fet] ian acne scorc
Gollnick et al. (29)	Minm:y<.:Iine	A:1aleic acitl	Minocyclinc vs lsotrctinom	6 months	months	A/aleic acitl (in antibiotics group)	Facial ksion count (incl subtypcs), invcstigator and parient•s global assessment
Gould et aC (30)	Tetracyclinc Erythromycin	13cnsoyl-peroxide Hibitanc Rctinoic aci<l _gel	110	io'%ri11::··'w· improvemt!nt . max 12 months	8 wet!ks	Contim1ed topical trcatmenL	Pen.:entage improvemen of", prt!\!ious grading
Hasibur et al. (3 I)	A/ithromyc.:in (puh;ecl) 1sotrt:1inoin	no	no	24 weeks or complete clearnnce	6 months	11(.)	Lesion cou11l
llayashi cl ul. (32)	\'1inocycline Roxithromyci n Faropcnem	no	vtinocydinc vs Roxit hromycin vs l·aropcncm	4 ,vecks	4 wet!ks	Was allowc<l, 34 patients uscd topical ant ibiot ics	Lc:-ion counl, pacrntngc rcduction ur inllammatory lcsion-., qualit) of lifc surwy. bactcrial examination tcscs

Table 2. Rcsults 1cgard ing mcthodolog.y or thc inclu<ll.Xl studies *(co11ti11uedJ*

Ilayashi ct al. (33)	Faropt.:ncm	A<lnpalcn1e	Ourntmn of antibtotic . Lopical monotherapy	2,4 \\ceks	2 wc1ek::. m one group	Adapalenc	Lcsion coLmt (incl subtypcs), pcrccntagc rcduction of inflammatOI)' lcsions, quality of lifo
Kin:ikd al. (34)	Ooxycycline	Dapsone	110	12 weeks	12 wccks	Uapsonc	SUIYCy Lcsion count (incl suhtypcs), IGA
Op1ica ct al. <35)	Tctracyclinc	Adapalcnc	Tctracyclinc vs lsotreLinoin	6 rnonrhs	2 monLhs	Adapalene (in antibiotics group)	Lesion counl (incl subtypcs). qucstionnairc. skin samples
Poulm ct al. (36)	Do.xycyclinc	,\<lapaknc+bcnzoyl-pcroxi<lc Vchiclc	Topical tt'Catmcnt during follo\\'-up	12 weeks	24 v..eck	Adapakme • beru:oyl-peroxid e Vchicle	Lesion count, pcrcentagc-global improvemcnt, lesion and IGA maintcn.mcc success rate, P acnes count
Rchman ct al. (37)	Azithromycin (pulscd)	Adapalcnc	Dosagc of azithromycin	3 months	6 months	Adapalene	Reduction in GAGS, phoLo analysis, self-assessmenL
Tan et al. (15)	Doxycycline	Adapalcnc I bcnzoyl-pcroxid c	Doxycyclinc. top1cal trcatmcnt as follow-up	12 ,vecks	2-l wccks	Adapalcnc-bcnzoy1-pcroxidc Vehicle	ICiA succcss r.tlc.:, lcsion count (incl subtypcs). treatment sal isfttct ion 1.1ucstionnairc
1l1ihouLol CI al. (38)	Doxycyclinc	Adapalcnc Vchiclc	Topical trcatmcnt <luring follow-up	12 wceks	16 \Vecks	Adapalene Vchicle	T.esion count, maintenance rate. global severity asscssmcnt

Trcatm<.:nt type

l11crc was a widc range of dilTerent treatmcnts studicd, both regarding oral antibiot1cs and comparisons. Dtffcrcm fo1111s of tetracyclines wcrc most conunon; other antibm:terial agent. e\aluatcd wcrc macrolidc • and faropenem.

·111i.: d1ffcrence!) in administere<ldosagc wcrc minor, mainly rcgarding pulsed UL.1thromyci11trcatmcnt. with ndnunistration vai)'mg from a fcw days per ,,.cck toa fcw day:-. pl.:r rnonth (28. 31. 37). l11e study cond ucted by Hasibur el al. (31) also <l1ffcn..:<l u1 the fact thal isotn.:tinoin in low-dosc was administered simultaneously as oral antibiotit:s lo all 111cluclcd patient·.

The prc<lomina1H top1cal trcatment in combinatinn with oral antibiotics ,,as adapalcnc. ,\ fe,, stucl ies d id not allow any uscd of topicnl treatment. Some st11d ies am1c<l Lo comprire the effoct s bet-..veen the usc of topical agents in combinrit ion with oral an11biot1cs. and the use of oral antibintics and a topical placebo. also rcfcrrcd toas a veh,ck. Haya:-.hi CL al. (32) allowed the use of .my top1cal treatmt:nt arter cessat,on of oral trcatment, mcluding topical antibiotics. 11u·cc studies (27, 36, 38) compart!d t!ffects of topical age111s comparcd to thcir ,·chicle m the maintenance phase, regardmg rccum:nce rnlc afler a successful a11tib1otics trcatmcnt.

11,e treatment length varicd and was bctwcen two weeks and ·ix months. The reasons for ccssation of therapy differecl, in somc studies thc lcngth was dccided at baseline as pan of lhe study design, whcrcas othcrs bascd the length on effect or treatment, and pattt.!nts wcre d1scon1inued ,,.·hen 80% improvcmcm or total clcarancc had been aclucvcd. ln somc stlld ies, o maximum treatment length was set but if impro, emcnt occum:d prior to this, treatment was discontinued early.

ln !>Ome stud1es. 110 comparisons wt:rc madc. but thcsc studies instead nimt!d Lo invc t,gatc if an effect coulcl be seen. or sarcty of thc cxamincd agents.

Length of follow-up

·111c length of follow-up arter concludc<l trcatmcnt with oral amibiotics varicd bctwccn two weeks to six months. Hayashi et al. (33) only iJlcludcd follow-up in one of threc

Lrcatmcnt groups. and had the shortes1follow-up Lime or two wcck.. Fcrahbas ct al. (26) also ha<l a two-wcck follow-up period in one of two trt:atment groups, \.Vhcrcas Lhcir olher group wu • followed for eight wccks post-trcatmcnt.

Long-tcrm cffccts after cessation of oral antibiotics

Scvcral different meLhods for evaluating outcomc wcre utilised in 1he included sLUdics. and add itionally with a large number of end-points. not all rcsults can be de ·cribed here A bricf summary is prcsented in order to generally show thcir findings.

In 1978. Gould er al. (30) conducred a cohort stu<ly. inve. tigating Lhc risk of rcbpsc post-trealment in patients with previously good rcsponsc to tctrncycline or ryLhromycin. and obscrved rec,HTence in 11 ouL of 16 patient. wirhin cight weeks. Rehman dal. (37) indicatcd rccu1Tcnce four months after ces aLion of thcrapy, but dcscribed nod iffen:!nce'" when comparing <losagc of pulscd nzithromycin. Hayash1 l!I al. (32) coul<l not indicate any difference in mainLcnancc bctwcen thrcc 1ypcs of an1ib101ics, mmucydine, roxithrmnycin, and faropcncm. ailbough. nu increase of inllammatory l s,ons \vas obsc1ved for either group <luring thc four wcck follow-up.

·nlc cffccts of topical agenL as maintenancc trcatmcnt aftcr cc sation of ornl antibiolic:-. ,-.crc rcponcd in scveral a11icles, with thr e fucusing rnainly 011 cffccts of topical agent· compure<lto il vchick. for adapalcnc (27, 38) or an adapalene and hem·oyl-pc1ox1dc combinat ion (36).'l71esc::all ·bowed lower lc!-.ion count and incrcascd maintenanc.:e rnLt:. c;im1larlj. Tan tL al. (15) studicd thc cffccts of an adapalc::ne and ben1:oyl-pcro:--1dc combmatton and sbo\\'ed continue<limprovcmcllt aftc1 oral antib1orics had been condu<le<l, and an tncrcascd IGA success. Similarly, in their m)n-comparam•c study. K irc.:ik et al. (34) invcsLigatcd maimcnancc trcatment \\'ith the lopical agent <lapsonc, and found a continued decrease in lesion counl in 1hc maintcnancc phase.

llm:c studics d id not allow any use of topical 1,-eatment during t hc follow-up pe1iod, allhough ncithcr of thcm indicated a decline in effoct. In the cross-ovcr study by Fcrahbas ct al. (26). no change in median acne score was shcm n m thc c1ghr-wcck follcm-up whcn using roxirlu-omycin. Uabaeinejad el al. (28) coul<lnot ind icatc an) clifft:rcnce in rccurrcncc ratc bctwccn thc group treated \\'ith doxycycline and

,l/ilhromycin. Has1bur el al. (3l) showcd a low race of rclap. c during the post-treatment follow-up, although usc<l a combination or pulso;:d azithromycin and isotrctinom. Howc\;er, none of the ·e three stud ics comparc<l thcir trcatmcnl rcgime wit h use of topical treatment.

In the two studies comparing isotrctinom to oral antibiotics, a tendency for improvcd mamtcnancc \.\a!-1 notc<l for isotretinoin. Gollnick et al. (29) detcctcd a discrctc incrcasc 111 numht!r of lt:sion • in the oral antibiot1cs group m thc maintcnancc phase. whero;:as a small reduct1on rn numbcr of comcdoncs was seen for isotrt!linoin. Oprica et al. (35) sho\, c<l a slight <lccrcase in face acne grad ing score for isotretinoin, and fo1 fcmak!-> Lrcatc<l "' 1th iM>lretinoin a contim1ed decreasc in lesion cotmt.

P. ac.:n s count n:mamecl stable po·r-trcatment with doxycyclinc \Vhcn using an adapalenc and bcnzoyl-pcroxidc combination. whereas it increased with its vchiclc <lcmonslraled h) Poulin et al. (36). Oprica et al. (35) showcd an incrcasc in numher of resi!'ltant P. acnes in the group prcviously trcatcd with tclracycline compared 10 1hose 1rcntcd with isotrctinom.

Discussion

Scvcral nictho<ls \\crc utifo,ed for grud ing acne and evaluating trcatmcnt outcomc. Trends rcgardmg optimnl maintcnancc trcatmcnt can be idcntiried. hut dut: to the dn crsny m mclhodology. it is challcnging to <lniw clinically relevant conclus1ons.

o standard mcthod for classification or evaluating outcome was idenrificd. l·or grad mg acne, mcthods utilised were predominantly divided into cithcr photograph1c, m, for e\ample Leecls grad ing ·cale (9) and Lccds rcviscd acne grading system (8), ur clinical. s11ch as lnvestigntors global asscssmcnt (IGA) prcscnted in full by Kircik et al. (34) or thc Japancsc acne st11dy group critcria (39). In 1997, Doshi el al. (40) intendcd to compnrc grading systems and crcatc a novcl clinical method, and suggested Glob.il acne gradmg ·ystem (GAGS), ,vhcrc lcsion counting was limited lo six locations on the facc, che·1 and back for simplicity and practical usc. Thcy also stated that methods u·inga clmical approach. rathcr than a photograph1c. are considered superfor duc to accuracy

and :-.pccd. Adapung thcsc mcthods 10 a clinical context is advantagcous, as many grad ing systems arc extensive and cime consuming, and time is not a rcsourcc availablt! in abundance in clinical pmctice. As mcntioncd in the introduction, Lehmann ct al. (7), in thcir cvidcnce review. idcntificd rnore than 25 mcthods for gra<ling acne. and fu1thermorc. ovcr 19 methods for counting lesions. ll1csc find ings un; in linc w1th the ,c ult of this cun-cnr study. ind icatiug a large number of mcthods presenl. As man) of thöc mcthoJs ::ire in somc scnsc subjective, comparing the resultii could be cons1dcrcd au arduous task. Sincc no gold standard for grading ac.:nc or mcasuring cffcct cx1st. it is imporrnnt for researchcrs to provide a clear definition of what mcthod is uciliscd in thcir ·1ud1es to l"aciliratc a comparison of cvidem:c.

Even though grading methods differ, all studies cxccpt one used 1hc tenns mild, moderate or severc. whcn classifying acne, and thc·c delini1ions arc gt:ncrally uscd clmu.:all) and in treatment guidclines (10). Lcsion count was anothcr common tcchnique, alLhough thc method of quantification might diffcr thus affccting thc comparability of the rcsults. Several studies calculated maintcnancc rnte or maintcnanct! succcss rote. nnd defim:d ,t in similar ways, bascd 011 assumpl1011s of clinicall) 1mpo11ant ..:ffcc1. M::iintcnance ol'50% unprovemem \\::IS constdt!red a rcalistic ,md asy 1.:1ilt!non lo mcasure t!llicacy of treatment by Alirczai et al. (27). which subsequcntl} \\ a!) based on the dcfin11ion of p·oria is rclapsl! prcviously propost:d by Gordon el al. (41). I r conscnsus n;gan.l rng methods of grad ing and evalualmg cffcct can be rcachcd. thi:-. multi improve both l'.V1dcnce and potcntiall) nlso thernpeut1c rcsults.

[nvestigating effects ur oral antibiotics in va1ying doses and <luration suggested no supcnor rcgime. howc, er. topical trcatmcnt after cc::;sat1on of oral therapy indicatcd improvcd maintcnancc. Poulin ct al. (36) desc1ibcd an increasc m P. acnes counl w hcn 110 topicnl trt!almcnt was used in the maintcnnnce phasc. Dccrcasing P. acnes count. and 1110!)1 importantly rt::-,istalll strai.ns, is one of thc aims with rcstnctmg oral antib1ot1cs. \llhough. an increasc of P. acnt!· resistant to roxithromycin \1,as nott:d hy Ha)ash1 et al. (-12). no <liffcrcnce was notcd rcgarding treatmcnt outcomt:. Hcncc. the corr..:lat1011 bct,\.cen presencc of rcsi tant P. acnes and outcomc 1s comple., and not fully undcli)tood. but resiscancc does not tran late direclly IO trcatmenl railurc sincc

antihiot1cs in acne cxcI1s cffccts in addit1on to bcing antibacterial (17). Co\'c cl al. (42) st.ited that a grcatcr numher or bacteria has no co1Tclat1on to increased scvcnt) ol' acne. and rhm chcrc is no relation betwecn a dccrcasc<l numher of viablc bactcna an<l 1rnpro\'l!<l outcome of trcmmcnl w1th oral antibiotics. Pcrson-to-pcrson transn11ssl011 of resistant bactcria has bccn suggested. rathcr than originating from treatmcIll ''ith ant1b1otics, an<l e, t:n a h1gher numbcr of resi<;tant bacteria colonisation was notcd m <lcnnatolog, ts comparcd with the gener.il population (19). However, somc cv1dcncc suggcst rcsistanl P. acnes is clinic.illy relevant, rcsulting in worscncd trcatmcnt dTc t ,md increascd risk or relapst! (17).

lrcacmcnt with oral antibiotics was in many of the studies concIude<l when suffic1cnt d'fect was obtaincd. rcsulting in some patients not rccciving any effcctivc trcatmcnt. and potcmially bcing prcscrihed antibiotics for long periods of timc with 110 furthcr Imprun mcnl. lsotretinoin then bccomcs a valid option, and bascd on ILs maimenancc dfrt:t comp:irt:d with oral anLibiotic:-., Lhis treatment could be con idered a morc beneficial solution. Oprica *et* al. {15) also showcd increased number of rcs,stant P. acnes dunng thc mainlenance phasc for tctracycline compared with isotrctinoin. [Iov,:c\'cr, 1-;oLrctinoin Is associated with increascd nsk ofadverse e,cnts, somc or these potl.!ntinll) lifc-thrcatening. Addit1onally, as fe\\ as two studies invcstigatcd Lhe effects of Is01rctmoin compared with antibiotics. Lhus limited data support this statemcnt.

Comhined ur.il contrnccptivcs is a11other effective treatmcm for acnt: regularly prescribcd to women (43). In this ClIrrcnt study. comparisons bctwccn oral contraccptive-.and antibiotics wcrc cxcluded, due to diffcrcncc in prescribing pattcm:-;. Oral conLraccptivcs arc. in many cases, prcscribcd continuously for many dccadcs. ,vhcrl!as antibiotic for disLinctly shorter duration. Although, strict compnnso11s \\ en: cxcluded. treatmenr with oral contraccpLives wns in many or the incl11ded srudlcs alkm ecl. In somc studics patients were only includcd if they were on oral contnu:eptiws for morc than thrcc or six months prior. /\ll patients on isotrcrinoin addilionally arc requ1rcd to Lake oral contraceptivcs, however, not all patients in the antibiot1cs groups. TI1c inconsistcncy in prescription can potentially have affcctcd thc results, since a

proportion of Lhc study population werc given nn ndditional cffccLivc trentmenl. In om: study. all women werc cxdudcd lo eliminate this confounder.

Follow-up ti.me wcU> shor1 in a fcw of Lhe indu<led studies, thus potentially affccting the omcomc. Rehman et al. (37) indicate<l that rclapsc commonly occurs around four months post-trcatment. yicl ding the studies with shortcr follow-up Lime d ifficult to mtt!rprel. AdditionaUy, ince guidclincs in Sweden today rccommend a maximum of two courses of oral antibiotics for no morc than three months. a post-treatmcnt mamtenance dTect of two weeks or less could be considered clinically irrele\ant sincc symptoms orten last for numerous ycars. Symptoms additionaUy flm:tuate naturaUy over timc. making it morc challcnging lo determinc treatment effcct. Fu11hcm1ore. n.:laci, cly rew stud1cs compared treatmcnt to placebo, and somc wcre even non-comparari,e, confcn-ing less robust c, idcncc. Many stud1cs induded small samplcs. potcntially affccung valid ity, and somc studies limitcd thci.r mvestigatiom, toa ce1tain suhgroup. such as only malt! or adoksccm patients, yicld ing rcsults harder Lo gcncralise.

In Swedish hcalthcare today. many oftbe aforernentioncd findings mal-.c up thc foundation or currcl\l guidelines. Topical trcatment dunng and afrcr treatrnent "1th oral antibiot1cs is ·trongly n:commcnded. fsotretinoin is utilised instcad of oral antihiotics, in sevt:n.! cascs of acne or when antibiotics prove msufficicnt, to decreusc thc usc of anttbacterial ugcnts, although, prescription is limill:!d to dcnnatologists in ord1.:r ıo mi11i111isc scrious ndvel"it cvcnrs. Considering thc abundance or literaturc inve·tiguting cffccts or acne trcauncnt. surprisingly fe\\ cvnluate long-tcm1 OLHcome. Guidel111cs arc ol'tc11 bascd on clinical cxpcricnce. which is of course immen ·cly valuablc but should be cons1derl!<l a complunent to scicntific cv1dencl!.

Acne vulgaris is a chronic cli<;casc and many patients havc symptoms ovcr a !arge proportion of their adolcsccm and young adult life (4}. Trl:!atmcm yicldng symptomnt1c rdi r fora fcw months can not be thc nim, instcad focus must lil! on maintcnancc Lo pro\ ide lasting cffccts. l\lorc studies invcstigating long-tcm1 cffi.:cts or cun-cnt guidelincs using standardised mcrhods of gmdmg scvcnty and e\alu.1ting outcome are needed.

Strcngths and \ eaknesscs

C ompnnng 1csulls rrom the includcd studies was difficult duc to varying definitions of scwnty and methods of cvaluating t!ITect. nnd thcrcforc no conclusions regartlmg lreatment outcome or quanlification of cffcct can be drawn. Although. the aim was 10 srnnmarisc the d1fference-. in previou studies. and since no !imitation. \\ ere made rl.!gard i11g sludy de·ign or comparisons. Li11s resulted in a broad overview of cmTCnt c, idcncl.!.

Another !imitation LO Lhis study is thc small numbt:r uf includcd studies. In lhe inclus1on nnd screening process difficulty in detennining whethcr long-tcnn follow-up had bccn stu<l1c<l or not wa-; noticcd·.111is may have cm1sed rclc\'ant articles wrongfully excludcl<l. D1.!tcnrnn111g whcthcr thc limik<l number of stud ics is d ue Lo the fact thnt ı\ \\ slud ,e e\'aluating maimenance has bccn conductcd or that they wcrc not identified i·d1fficult 10 say. J\dd itional art1clcs wcrc fouucl when rcviewing rcl't!rences in Litcraturc nddressmg the suhjed and thus includcd in the as es·ment of cligibilily. A fler morc c tcm,ive reading, no förthcr citations were identified indieating that mo t rclc\ant o;tud1es \\ere includcd

Screening of thc artides \Vas perfom1ed by onc 111vcst igator, result ing in a 11s ur bia-;. lthough, this inlmduced a stringcncy in thc evaluation of cligibility, which could be consi<lcred a strcnl,.rth.

o limitat mn was set for ycar or puhlicat ion. which led lo all historie studies bci11g md11dt!d. the oldcst from 1978. Even though thc anLibiotic tablet remain. tlie same. methods for prcscrihing cliffers. histoncally no !imitation for duration or numbcr ol coun,cs was applied Additionally, prevalence of resistant bacteria 1,,va • lowcr and thcrd'ore an1ibiot1cs potcntially more effective. The qualily of the older tudics might he queo;tionecl duc to less clcarly described mcthodology and no ethical npprO\al. Although. quc1lity could also he quest ioned for somc of the more recently puhlished art ides from less rcnowned journals, some conrnining contrnd icting infonnat ion. Tht! puqmse or not sett ing !imitations fort he search critcria was to gain an ove1vicw of all that has previously bccn stu<lied.

Conflict of interest

The author declares no competing interests.

Conclusion

\\ ht!n in,cstigatmg trt!atmcnt with or.il antibiotics for acne vulgaris. several mcthod for grad mg and e\aluatmg cffect::. wcrc utih ed. No gold standard ,, as idcnt1f1ed. although sim1laritit:s wcrc seen, sud1as classifying acne as mild, moderate or ·e,ere. \1cthods for e, aluaring outcom<.wcrc in several cascs eon·tructcd by the rt!searchcrs resulting 111 d1fficultics in comparing cffccts.

Tmpro,·cd mamttmanccdfccr was suggcstcd for follO\\.-up treatment with topical agents and for 1sotrctinoin, in rt!gards to relapse and prcscnce of n::s,stant P. acnes. ll1c role of P. acnes m relation to acne severity and treatment outcome is not l'ully unden,tood. but a negative <.:orrclation has hccn implied.

Evidencc supporting ornl antibiotics being cffccth·e in trcating acne is abundant, although data rcgarding duration of effect arc scarcc and inconclusivc. Standardbcd mcthods for grading and evaluating cffccts ,:irt! rt:quircd to fäcihtatc data synthes1s m order to support recommendations of best clinical practice

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