

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021549
Article Type:	Research
Date Submitted by the Author:	09-Jan-2018
Complete List of Authors:	Li, Changqiang ; the Affiliated Hospital of Southwest Medical University, Department of Dermatology Chen, Jianmei ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Wang, Wo ; University-Town Hospital of Chongqing Medical University, Mental Health Center Ai, Ming ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Zhang, Qi ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Kuang, Li
Keywords:	Acne < DERMATOLOGY, Depression & mood disorders < PSYCHIATRY, ORAL MEDICINE

SCHOLARONE™
Manuscripts

1
2
3 **Use of isotretinoin and risk of depression in patients with acne: a systematic review and**
4
5
6 **meta-analysis**
7

8 Changqiang Li², Jianmei Chen¹, Wo Wang³, Ming Ai¹, Qi Zhang¹, Li Kuang^{1*}
9

10
11 ¹Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical University,
12
13 Chongqing 400016, China
14

15
16 ²Department of Dermatology, the Affiliated Hospital of Southwest Medical University,
17
18 Luzhou646000, China
19

20
21 ³Mental Health Center, University-Town Hospital of Chongqing Medical University,
22
23 Chongqing 401331, China
24
25

26
27
28 ***Corresponding author:**
29

30 Li Kuang
31

32
33 Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical University,
34
35 Chongqing 400016, China
36

37
38 Tel: +86-13908379733
39

40
41 Fax: +86-21-64085875
42

43
44 Email: kuangli0308@163.com
45
46

47
48 **Running title:** isotretinoin and risk of depression in patients with acne
49
50
51
52
53
54
55
56
57
58

ABSTRACT

Objectives: Oral isotretinoin is the first-line treatment of severe acne vulgaris, while isotretinoin may associate with depressive disorders risk. The purpose of this study was to investigate the association between the use of isotretinoin and risk of depression in patients with acne vulgaris.

Design: meta-analysis. The standardized mean difference (SMD) and the relative risk (RR) were used employed for data synthesis by using random-effects model. **Setting:** Studies were identified by electronic searches of PubMed, Embase, and the Cochrane Library up to December 2017.

Participants: acne patients.

Interventions: Studies comparing isotretinoin with other interventions in acne patients were included.

Results: Twenty studies were selected. The analysis of 17 studies showed that the use of isotretinoin was significantly associated with improved symptoms measured on the depression scales compared with the baseline before treatment [SMD = -0.33, 95% confidence interval(CI) -0.51 to -0.15, $P < 0.05$; $I^2 = 76.6\%$, $P < 0.05$]. Four studies were related to the analysis of the risk of depression, and the pooled data indicated the use of isotretinoin was not associated with the risk of depressive disorders (RR = 1.15, 95% CI 0.60–2.21, $P = 0.14$). Further, the risk of depressive disorders was increased when pooled retrospective studies (RR = 1.39, 95% CI 1.05–1.84, $P = 0.02$), but the use of isotretinoin

1
2
3 has no significant effect on the risk of depressive disorders when pooled prospective studies
4
5
6 (RR = 0.85, 95% CI 0.60–2.21, $P = 0.86$).
7

8 **Conclusions:** The findings of this study suggested acne patients received isotretinoin was
9
10 associated with significantly improved depression symptoms. However, it may play an
11
12 important role on the progression of depression. Future randomized controlled trials are
13
14 needed to verify the present findings.
15
16
17
18
19
20

21 **Strengths and limitations of this study**

- 22 1. Most included studies were prospectively designed, and the quality of included studies
23
24 was largely moderate to high.
25
26
- 27 2. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses.
28
29
- 30 3. The small sample sizes of some included studies might have limited the statistical power
31
32 and increased the chance of missing small effects.
33
34
- 35 4. No RCT was available so far, which was a major drawback for studies on this topic.
36
37
- 38 5. The treatment duration, drug dose, and depression scale varied between different studies.
39
40
41
42
43

44 **Keywords:** acne; depression; isotretinoin; meta-analysis
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit of the face, neck, chest, and back ¹. As a pleomorphic skin disease, it may present as noninflammatory lesions (open and closed comedones) or inflammatory lesions (papules, pustules, or nodules) ². It is the most common skin disease around the world, with an estimated prevalence of 70%–87% ³. The economic burden of acne was substantial. The cost is estimated to exceed \$1 billion per year in the United States for direct acne therapy, with \$100 million spent on various acne products ⁴. Acne vulgaris may cause cosmetic defects and significantly impact on the quality of life ⁵. It may provoke a wide range of mental problems, including depression, anxiety, poor self-esteem, social-phobia, and even suicide attempts ⁶.

The optimal treatment approach is dependent on the morphology and severity of acne. Mild cases are suggested to be treated with topical retinoids. For moderate cases, systemic drugs are always needed, including oral antibiotics, hormonal therapy, and oral retinoids. However, for severe or resistant moderate acne, isotretinoin is the treatment of choice ^{1,2,4,7}. Isotretinoin is a vitamin A-derivative 13-*cis*-retinoic acid, which is the most effective therapy for acne to date. It targets all four processes during acne development, including normalization of follicular desquamation, reduction of sebaceous gland activity, inhibition of the proliferation of *Propionibacterium acnes*, and anti-inflammatory effects ^{2,7,8}. The meta-analysis suggested that isotretinoin cured around 85% of patients after an average treatment course of 4 months ⁹.

1
2
3 Depressive disorders are highly prevalent in the Western world. The lifetime prevalence of
4
5
6 major depressive disorders in the United States and Western Europe is around 13%–16%¹⁰.
7
8
9 The frequency of depressive disorders during the use of isotretinoin varies from 1% to 11%
10
11¹¹. Theoretically, effective treatment may lead to an improvement in depressive symptoms
12
13 of acne patients. However, the use of systemic isotretinoin itself may potentially increase
14
15 the risk of depression¹². Experimental studies showed that isotretinoin could affect the
16
17 central nervous system and was involved in the pathogenesis of depression¹³. However,
18
19 some researchers disputed that the risk was extremely small and might be influenced by the
20
21 background risk or nondrug confounding factors¹². The evidence for this controversy
22
23 remained incomplete and unclear. Therefore, this systematic review and meta-analysis was
24
25 performed to explore the association between the use of isotretinoin and risk of depression
26
27 among acne patients. Further, whether this relationship is differing in patients with specific
28
29 characteristics were also performed.
30
31
32
33
34
35
36
37
38

39 **METHODS**

40 **Literature search**

41
42 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was
43
44 followed to conduct this meta-analysis¹⁴. A literature searches up to December 2017 was
45
46 performed, using PubMed, Embase, and the Cochrane Library. The following groups of
47
48 keywords were used in our search: (“depression” OR “depressive”) AND “acne” AND
49
50 “isotretinoin.” Also, the manual search of references listed in included studies and published
51
52
53
54
55
56
57
58
59
60

1
2
3 reviews were also performed to search for potentially eligible studies. The language was
4
5
6 restricted to English.
7

8 9 **Selection criteria**

10
11 Studies were included if they fulfilled the following criteria: (1) being randomized
12
13 controlled trial (RCT), prospective or retrospective study, nested case-control study, or
14
15 population-based case-control study; (2) comparing the outcomes before and after the use
16
17 of isotretinoin in acne patients; or comparing isotretinoin with other treatment regimens in
18
19 patients with acne; (3) presenting the change in depressive symptoms measured by a
20
21 continuous depression scale¹⁵; or reporting the number of depressive patients before and
22
23 after the use of isotretinoin; or directly presenting the relative risk (RR), odds ratio (OR), or
24
25 hazard ratio (HR) between the use of isotretinoin and risk of depression.
26
27
28
29
30

31 32 **Data extraction and quality assessment**

33
34 Two authors independently assessed the titles and abstracts for eligibility and extracted data
35
36 in standardized electronic tables. The following data were extracted from included studies:
37
38 publication year, author, study design, sample size, participant sex and age, severity of acne,
39
40 compared groups, dose and duration of isotretinoin, and depression assessment tool. The
41
42 quality of included studies was assessed by the 9-star Newcastle-Ottawa Scale. This scale
43
44 evaluated the study quality based on three parameters: selection, comparability, and
45
46 exposure (case-control study) or outcome (cohort study). A maximum of 4 points was
47
48 assigned for the item of selection, 2 points for comparability, and 3 points for
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 exposure/outcome ¹⁶. Studies were deemed as high quality for a score of 8–9, moderate
4
5 quality for a score of 6–7, and low quality for a score ≤ 5 .
6
7

8 **Statistical analysis**

10
11 The continuous outcome of interest was the alteration in depressive symptoms assessed by a
12
13 continuous depression scale after the use of isotretinoin. For the continuous parameter of
14
15 depression score, the mean and standard difference (SD) of the score was extracted. The
16
17 standard mean difference (SMD) was used as the outcome measure. The SMD was a
18
19 unitless effect size estimate, which was the mean difference in the depression score between
20
21 the compared groups divided by the pooled SD of the distribution of the score used in the
22
23 study. The conversion of median (range/ interquartile range) to mean \pm SD was done by a
24
25 previously proposed method ¹⁷. The binary outcome of interest was the number of
26
27 participants whose conditions were regarded as depression. RR and its corresponding 95%
28
29 confidential interval (CI) were used as the outcome measure. HR was regarded as
30
31 equivalent to RR in cohort studies. Given the overall low incidence of depression among the
32
33 general population, OR was assumed to be an accurate estimate of RR. It was preferred to
34
35 use the effect measures that reflected the greatest degree control for confounding factors.
36
37 Both adjusted and crude data were analyzed. When data on different subgroups were
38
39 reported by the same cohort, they were first pooled by the fixed-effects model. As the
40
41 random-effects model was more robust than the fixed-effects model, the DerSimonian–
42
43 Laird random-effects model was used to calculate the overall effect estimates for the
44
45 association between the use of isotretinoin and risk of depression ¹⁸. The heterogeneity was
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 evaluated by the Cochrane Q test and the I^2 statistic. Heterogeneity was considered low,
4 moderate, or high for $I^2 < 25\%$, $25\% - 50\%$, and $> 50\%$, respectively^{19,20}. Subgroup analyses
5
6 were conducted based on the following confounders: region, study design, sample size,
7
8 female percentage, and depression scale. Furthermore, meta-regression analyses were
9
10 performed for the continuous confounders of sample size and female percentage. A
11
12 sensitivity analysis was conducted by excluding a single study at a time. Also, a sensitivity
13
14 analysis was conducted using the weighted mean difference (WMD) as the effect estimate
15
16 for studies employing the same depression symptom scale. The publication bias was
17
18 visually assessed by the construction of funnel plot and statistically assessed by the Begg
19
20 and Egger regression asymmetry tests^{21,22}. All statistical analyses were conducted using the
21
22 software Stata 12.0 (StataCorp, TX, USA). A *P* value less than 0.05 was considered
23
24 statistically significant.
25
26
27
28
29
30
31
32
33
34
35
36

37 RESULTS

38 Study selection

39
40 A total of 632 records were retrieved from the electronic search, including 145 studies from
41
42 PubMed, 469 records from Embase, and 18 records from the Cochrane Library. After
43
44 screened by titles and abstracts. Five hundred and seventy-one were excluded with the
45
46 following reasons: reviews, editorials, case reports, or irrelevant studies, leaving 61 studies
47
48 for full-text review. Nine cross-sectional studies, 19 studies without sufficient data, and 13
49
50 studies were review, editorial, or comments were excluded. Finally, 20 studies were pooled
51
52
53
54
55
56
57
58
59
60

1
2
3 into the meta-analysis²³⁻⁴³. A flow diagram of the study selection process is depicted in
4
5
6 Figure. 1.
7

8 **Study characteristics**

9
10 The characteristics of the included 20 studies are shown in Table 1. Jick et al. reported two
11
12 independent cohorts²⁴, which were analyzed separately. Except for two retrospective
13
14 studies identifying depressive patients by the International Classification of Diseases code²⁴,
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

1
2
3 moderate and severe acne³⁵. Fakour et al. showed data for males and females separately³⁷.
4
5
6 Kaymak et al. reported depression scores measured by Beck Depression Inventory (BDI)
7
8 and hospital anxiety and depression scale-depression (HADS-D) scales³³. These subgroup
9
10 data were all pooled into the overall analysis. Compared with the baseline condition before
11
12 therapy, the use of isotretinoin was associated with significant improvement in depressive
13
14 symptoms (SMD = -0.33, 95% CI -0.51 to -0.15, $P < 0.05$) (Figure. 2). Highly significant
15
16 heterogeneity was revealed ($I^2 = 76.6\%$, $P < 0.05$).
17
18

19
20
21 In the sensitivity analysis, the overall effect was not substantially altered when excluding
22
23 any single study. In the meta-regression analysis, the number of included participants ($P =$
24
25 0.995) and the female proportion ($P = 0.56$) did not account for the source of heterogeneity.
26
27

28
29 Data on subgroup analyses are shown in Table 2. The pooled effect estimate remained
30
31 significant for 14 European studies (SMD = -0.35, 95% CI -0.51 to -0.19, $P < 0.05$), with
32
33 moderate heterogeneity ($I^2 = 46.3\%$). However, the analysis of three Asian studies did not
34
35 show significant result (SMD = -0.18, 95% CI -0.81 to 0.45, $P = 0.57$; $I^2 = 94.4\%$). Only 1
36
37 study conducted in North America and Africa, respectively. We noted the use of isotretinoin
38
39 has no significant effect on depressive symptoms in North America (SMD = -0.23, 95%CI
40
41 -0.59 to 0.13; $P = 0.21$), while it could improve depressive symptoms in Africa (SMD =
42
43 -0.74, 95%CI -1.22 to -0.26, $P < 0.05$). The pooled results remained significant for studies
44
45 using HADS-D (SMD = -0.57, 95% CI -0.83 to -0.31, $P < 0.25$; $I^2 = 27.2\%$), and those
46
47 using the Center for Epidemiological Studies Depression scale (CES-D) (SMD = -0.27, 95%
48
49 CI -0.52 to -0.02, $P < 0.05$; $I^2 = 0\%$). However, the pooled effect turned to be
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 non-significant for studies using the BDI scale (SMD = -0.15, 95% CI -0.36 to 0.06, $P =$
5
6 0.17; $I^2 = 62.4\%$) and those using the Hamilton Rating Scale (HRS) (SMD = -0.55, 95% CI
7
8 -1.56 to 0.46, $P = 0.29$; $I^2 = 96.6\%$). The pooled effects were significant for both studies of
9
10 smaller sample size (SMD = -0.38, 95% CI -0.65 to -0.12, $P < 0.05$) and those with larger
11
12 sample size (SMD = -0.29, 95% CI -0.54 to -0.04, $P < 0.05$). Results for different
13
14 proportions of females did not show a significant difference. The funnel plot appeared to be
15
16 symmetrical (Figure. 3). No publication bias was revealed by the Egger's test ($P = 0.76$) or
17
18 by the Begg test ($P = 0.87$).

19
20
21 Also, the sensitivity analysis was performed by pooling the WMD for studies using the
22
23 same scale. The pooled results were non-significant for studies using the BDI scale (WMD
24
25 = -0.84, 95% CI -2.05 to 0.38, $P = 0.18$; $I^2 = 62.2\%$, $P < 0.05$) (Figure. 4), and those using
26
27 HRS (WMD = -1.91, 95% CI -5.44 to 1.63, $P = 0.29$; $I^2 = 97.3\%$, $P < 0.05$). In contrast, the
28
29 pooled WMDs were significant for studies using HADS-D (WMD = -2.06, 95% CI -3.42
30
31 to -0.70, $P < 0.05$; $I^2 = 66.0\%$, $P < 0.05$), studies using CES-D (WMD = -1.88, 95% CI
32
33 -3.64 to -0.11, $P < 0.05$; $I^2 = 0\%$, $P = 0.63$).

41 42 **Use of Isotretinoin and risk of depression**

43
44 Two retrospective studies showed the adjusted RR for the association between the use of
45
46 isotretinoin and risk of depression^{24, 31}. Jick et al. presented data for two independent
47
48 cohorts. The overall result of three cohorts showed that the use of isotretinoin was
49
50 associated with an increased risk of depression (RR = 1.39, 95% CI 1.05–1.84, $P = 0.02$;
51
52 Figure. 5), and no significant heterogeneity was shown ($I^2 = 0.0\%$, $P = 0.50$). However,
53
54
55
56
57
58
59
60

1
2
3
4 there was no significant difference for the relationship between isotretinoin use and the risk
5
6 of depression when pooled two prospective studies (RR = 0.85, 95% CI 0.60–2.21, $P = 0.86$;
7
8 Figure. 5), and substantial heterogeneity was observed ($I^2 = 61.4\%$, $P = 0.11$). The funnel
9
10 plot appeared to be symmetrical (Figure. 6), and the Egger's test ($P = 0.76$) or the Begg test
11
12 ($P = 1.00$) suggested no evidence of potential publication bias.
13
14
15

16 17 18 19 **DISCUSSION**

20
21 The risk of depression associated with the use of isotretinoin in patients with acne has been
22
23 a major concern for a long time. Previous data showed conflicting and inconsistent results.
24
25 Two previous systematic reviews on similar topic were detected^{13, 44}. Although
26
27 comprehensive scenarios were presented, they failed in conducting data synthesis to obtain
28
29 pooled results. This meta-analysis that assessed the association between the use of
30
31 isotretinoin and risk of depression. It had several strengths as follows. A comprehensive
32
33 database search of worldwide cohorts was conducted, enrolling a large number of
34
35 participants. The quality of included studies was largely moderate to high. Most included
36
37 studies were prospectively designed. The association was investigated in several aspects.
38
39 The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses. The
40
41 present findings showed that isotretinoin was beneficial rather than harmful for the
42
43 improvement in depressive symptoms for acne patients (SMD = -0.33 , $P < 0.05$). When
44
45 employing WMD as the effect estimate to assess studies using the same depression scale,
46
47 the benefit remained marked for studies using HADS-D and CES-D. Although no
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 statistically significant data were shown for studies of BDI scale or HRS, the pooled WMD
4
5
6 was in favor of patients after the use of isotretinoin. In risk assessment, the summary RR
7
8 showed that the use of isotretinoin increased the risk of depression for patients with acne
9
10
11 when pooled retrospective studies, while this increased risk was not observed in prospective
12
13
14 studies.

15
16 Vallerand conducted a systematic review based on 11 trials to evaluate the efficacy and safety
17
18 of oral isotretinoin for acne, they point oral isotretinoin significantly reduced acne lesion
19
20 counts, while greater number of psychiatric adverse events (Depressed mood, fatigue,
21
22 hallucination, insomnia, lethargy) was found (32 versus 19). However, this study was not
23
24 provided the result by data synthesis⁴⁵. Further, Huang et al conducted a meta-analysis based
25
26 on 31 studies and suggested the use of isotretinoin was not affected the incidence of
27
28 depression. Further, they point out the treatment of acne could ameliorate depressive
29
30 symptoms. However, the study summary the investigated outcomes just stratified by
31
32 depression assessment tool, whether these relationships are differing according to region,
33
34 study design, sample size, and female percentage were not illustrated⁴⁶. We therefore
35
36 conducted this comprehensive, quantitative synthesis based on available studies to evaluate
37
38 any potential impact of the use of isotretinoin on the outcomes of depression incidence and
39
40 change in the depression score.
41
42
43
44
45
46
47
48

49 The concern for negative mood may arise from a series of experimental studies. Oral
50
51 isotretinoin significantly suppressed cell division in the hippocampus and severely disrupted
52
53 the learning capacity of mice⁴⁷. Bremner et al. found that isotretinoin, but not antibiotics,
54
55
56
57
58
59
60

1
2
3
4 was associated with decreased brain metabolism in the orbitofrontal cortex, which was
5
6 known to mediate depression symptoms⁴⁸. O'Reilly et al. proved that isotretinoin altered
7
8 intracellular serotonin, increased 5-HT1A receptor, and serotonin reuptake transporter
9
10 levels *in vitro*⁴⁹. Thus, theoretically, isotretinoin itself may cause depressive disorders.
11
12 However, the potentially increased risk of depression could be compensated by the
13
14 treatment effects of isotretinoin for acne patients. Most acne patients were worried about
15
16 their appearances, which might lead to a series of psychological disorders. It was inferred
17
18 that the improvement in depression symptoms after the use of isotretinoin might be
19
20 attributed to the treatment success. Also, isotretinoin had a gradual effect on mood over
21
22 time, which was not an acute event⁵⁰.

23
24
25
26
27
28
29 Of note, the controversy over this topic was complicated by various confounding
30
31 psychosocial and clinical factors. Aktan et al. suggested that adolescent girls were more
32
33 vulnerable compared with boys to the negative psychological effects of acne⁵¹. Women
34
35 with acne were significantly more embarrassed compared with males about their skin
36
37 disease. A large database study showed that female gender and acne could jointly increase
38
39 the risk of depression⁵². However, the role of gender was not revealed in meta-regression
40
41 and subgroup analyses. Acne itself can exert different impacts on individual patients. The
42
43 lack of knowledge, especially about prognosis, may be a source of depression^{24, 53}.
44
45 Approximately one-fifth of acne patients suffered from psychiatric disorders³³. Better
46
47 health education and care were important components for treating acne patients. They help
48
49 eliminate the patients' misconceptions about the disease and unrealistic treatment
50
51
52
53
54
55
56
57
58
59
60

1
2
3 expectations ⁵⁴. The psychological interventions may vary between different clinical
4
5 settings and lead to a bias for the effect of isotretinoin. Besides, data on the efficacy or side
6
7 effect of the use of isotretinoin were insufficient in most included studies. Isotretinoin may
8
9 cause teratogenic toxicity. Contraceptives are recommended for female users of fertile age
10
11 to prevent pregnancy until the completion of treatment ⁴¹. The levels of blood cholesterol
12
13 and liver enzymes may be abnormal and should be monitored during the treatment phase ⁵⁵.
14
15 Several shortcomings regarding this meta-analysis should be explained. The sample sizes of
16
17 some included studies were still small, which might have limited the statistical power and
18
19 increased the chance of missing small effects. Cohort studies may have a bias caused by
20
21 participant selection and confounding factors. Most studies compared the before- and
22
23 after-treatment data. Ideally, RCTs comparing isotretinoin with placebo or other agents may
24
25 provide more robust findings. However, leaving moderate-to-severe acne patients without
26
27 the use of isotretinoin maybe unfair and even not ethical. However, no RCT was available
28
29 so far, which was a major drawback for studies on this topic. Additionally, the treatment
30
31 duration, drug dose, and depression scale varied between different studies. The acne
32
33 severity or the dose of isotretinoin varied and was not reported by several studies. Patients
34
35 with severe acne or scars or those unresponsive to therapy may have a worse depressive
36
37 mood. However, the analyses for these confounding factors were insufficient in most
38
39 studies. Approximately one-fifth of acne patients suffered from psychiatric disorders ³³.
40
41 Also, some studies were sponsored by corporations ²⁴, which might have underestimated the
42
43 incidence of depressive disorders. Finally, although greater risk of depression was founded
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 in isotretinoin used in pooled retrospective studies, whereas selection and recall biases might
4
5
6 affect the incidence of depression. Further, these conclusions may be unreliable since
7
8 smaller cohorts were included in such subsets.
9

10
11 This meta-analysis showed that patients may have improved depressive symptoms after the
12
13 use of isotretinoin. Psychologists are encouraged to participate in the management of acne
14
15 patients. Further, the use of isotretinoin in acne patients did not contribute to the development
16
17 of depression. While the summary results of retrospective studies suggested the use of isotretinoin
18
19 in acne patients might increase risk of depression. Future prospective controlled trials are
20
21 warranted to verify the present findings.
22
23
24
25
26
27
28

29 **Funding**

30
31 Not applicable.
32
33
34
35
36

37 **A competing interests statement.**

38
39 Not declared.
40
41
42
43

44 **Author's contribution**

45
46 CQL and LK contributed to conception and design; CQL, JMC, WW, MA, QZ and LK
47
48 contributed to acquisition of data, or analysis and interpretation of data; CQL, JMC, WW,
49
50 MA, QZ and LK have been involved in drafting the manuscript or revising it critically for
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

important intellectual content; all authors have given final approval of the version to be published.

A data sharing statement

No additional data are available.

For peer review only

REFERENCES

- 1 Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet* 2012;**379**:361-72.
- 2 Katsambas AD, Stefanaki C, Cunliffe WJ. Guidelines for treating acne. *Clin Dermatol* 2004;**22**:439-44.
- 3 Dreno B, Poli F. Epidemiology of acne. *Dermatology* 2003;**206**:7-10.
- 4 James WD. Clinical practice. Acne. *N Engl J Med* 2005;**352**:1463-72.
- 5 Thomas DR. Psychosocial effects of acne. *J Cutan Med Surg* 2004;**8 Suppl 4**:3-5.
- 6 Saitta P, Keehan P, Yousif J, et al. An update on the presence of psychiatric comorbidities in acne patients, Part 2: Depression, anxiety, and suicide. *Cutis* 2011;**88**:92-7.
- 7 Dawson AL, Dellavalle RP. Acne vulgaris. *BMJ* 2013;**346**:f2634.
- 8 Chivot M. Retinoid therapy for acne. A comparative review. *Am J Clin Dermatol* 2005;**6**:13-9.
- 9 Wessels F, Anderson AN, Kropman K. The cost-effectiveness of isotretinoin in the treatment of acne. Part 1. A meta-analysis of effectiveness literature. *S Afr Med J* 1999;**89**:780-4.
- 10 Kurek A, Johanne Peters EM, Sabat R, et al. Depression is a frequent co-morbidity in patients with acne inversa. *J Dtsch Dermatol Ges* 2013;**11**:743-9, 43-50.
- 11 Borovaya A, Olisova O, Ruzicka T, et al. Does isotretinoin therapy of acne cure or cause depression? *Int J Dermatol* 2013;**52**:1040-52.
- 12 Wolverton SE, Harper JC. Important controversies associated with isotretinoin therapy for acne. *Am J Clin Dermatol* 2013;**14**:71-6.

- 1
2
3
4 13 Kontaxakis VP, Skourides D, Ferentinos P, et al. Isotretinoin and psychopathology: a
5
6 review. *Ann Gen Psychiatry* 2009;**8**:2.
7
8
9 14 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews
10
11 and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.
12
13
14 15 Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck
15
16 Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale
17
18 (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale
19
20 (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)*
21
22 2011;**63 Suppl 11**:S454-66.
23
24
25
26 16 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing
27
28 the quality of nonrandomised studies in meta-analyses.
29
30 http://www.ohrica/programs/clinical_epidemiology/oxfordasp
31
32
33
34 17 Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from
35
36 the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*
37
38 2014;**14**:135.
39
40
41
42 18 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*
43
44 1986;**7**:177-88.
45
46
47 19 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses.
48
49 *BMJ* 2003;**327**:557-60.
50
51
52 20 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*
53
54 2002;**21**:1539-58.
55
56
57
58
59
60

- 1
2
3
4 21 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for
5
6 publication bias. *Biometrics* 1994;**50**:1088-101.
7
- 8
9 22 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple,
10
11 graphical test. *BMJ* 1997;**315**:629-34.
12
- 13
14 23 Kellett SC, Gawkrödger DJ. The psychological and emotional impact of acne and the
15
16 effect of treatment with isotretinoin. *Br J Dermatol* 1999;**140**:273-82.
17
- 18
19 24 Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression,
20
21 psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* 2000;**136**:1231-6.
22
- 23
24 25 Ng CH, Tam MM, Celi E, et al. Prospective study of depressive symptoms and quality of
25
26 life in acne vulgaris patients treated with isotretinoin compared to antibiotic and topical
27
28 therapy. *Australas J Dermatol* 2002;**43**:262-8.
29
- 30
31 26 Ferahbas A, Turan MT, Esel E, et al. A pilot study evaluating anxiety and depressive
32
33 scores in acne patients treated with isotretinoin. *J Dermatolog Treat* 2004;**15**:153-7.
34
- 35
36 27 Chia CY, Lane W, Chibnall J, et al. Isotretinoin therapy and mood changes in adolescents
37
38 with moderate to severe acne: a cohort study. *Arch Dermatol* 2005;**141**:557-60.
39
- 40
41 28 Kellett SC, Gawkrödger DJ. A prospective study of the responsiveness of depression and
42
43 suicidal ideation in acne patients to different phases of isotretinoin therapy. *Eur J*
44
45 *Dermatol* 2005;**15**:484-8.
46
- 47
48 29 Kaymak Y, Kalay M, Ilter N, et al. Incidence of depression related to isotretinoin
49
50 treatment in 100 acne vulgaris patients. *Psychol Rep* 2006;**99**:897-906.
51
- 52
53 30 Cohen J, Adams S, Patten S. No association found between patients receiving
54
55
56
57
58
59
60

- 1
2
3 isotretinoin for acne and the development of depression in a Canadian prospective
4
5 cohort. *Can J Clin Pharmacol* 2007;**14**:e227-33.
6
7
- 8
9 31 Azoulay L, Blais L, Koren G, et al. Isotretinoin and the risk of depression in patients
10
11 with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008;**69**:526-32.
12
- 13
14 32 Bozdag KE, Gulseren S, Guven F, et al. Evaluation of depressive symptoms in acne
15
16 patients treated with isotretinoin. *J Dermatolog Treat* 2009;**20**:293-6.
17
- 18
19 33 Kaymak Y, Taner E, Taner Y. Comparison of depression, anxiety and life quality in acne
20
21 vulgaris patients who were treated with either isotretinoin or topical agents. *Int J*
22
23 *Dermatol* 2009;**48**:41-6.
24
- 25
26 34 Rehn LM, Meririnne E, Hook-Nikanne J, et al. Depressive symptoms and suicidal
27
28 ideation during isotretinoin treatment: a 12-week follow-up study of male Finnish
29
30 military conscripts. *J Eur Acad Dermatol Venereol* 2009;**23**:1294-7.
31
- 32
33 35 Simic D, Situm M, Letica E, et al. Psychological impact of isotretinoin treatment in
34
35 patients with moderate and severe acne. *Coll Antropol* 2009;**33 Suppl 2**:15-9.
36
- 37
38 36 McGrath EJ, Lovell CR, Gillison F, et al. A prospective trial of the effects of isotretinoin
39
40 on quality of life and depressive symptoms. *Br J Dermatol* 2010;**163**:1323-9.
41
- 42
43 37 Fakour Y, Noormohammadpour P, Ameri H, et al. The effect of isotretinoin (roaccutane)
44
45 therapy on depression and quality of life of patients with severe acne. *Iran J Psychiatry*
46
47 2014;**9**:237-40.
48
- 49
50 38 Ergun T, Seckin D, Ozaydin N, et al. Isotretinoin has no negative effect on attention,
51
52 executive function and mood. *J Eur Acad Dermatol Venereol* 2012;**26**:431-9.
53
54
55
56
57

- 1
2
3
4 39 Ormerod AD, Thind CK, Rice SA, et al. Influence of isotretinoin on hippocampal-based
5
6 learning in human subjects. *Psychopharmacology (Berl)* 2012;**221**:667-74.
7
8
9 40 Yesilova Y, Bez Y, Ari M, et al. Effects of isotretinoin on obsessive compulsive
10
11 symptoms, depression, and anxiety in patients with acne vulgaris. *J Dermatolog Treat*
12
13 2012;**23**:268-71.
14
15
16 41 Marron SE, Tomas-Aragones L, Boira S. Anxiety, depression, quality of life and patient
17
18 satisfaction in acne patients treated with oral isotretinoin. *Acta Derm Venereol*
19
20 2013;**93**:701-6.
21
22
23 42 Gnanaraj P, Karthikeyan S, Narasimhan M, et al. Decrease in "Hamilton Rating Scale for
24
25 Depression" Following Isotretinoin Therapy in Acne: An Open-Label Prospective
26
27 Study. *Indian J Dermatol* 2015;**60**:461-4.
28
29
30
31 43 Suarez B, Serrano A, Cova Y, et al. Isotretinoin was not associated with depression or
32
33 anxiety: A twelve-week study. *World J Psychiatry* 2016;**6**:136-42.
34
35
36
37 44 Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with
38
39 isotretinoin: a systematic review. *Semin Cutan Med Surg* 2007;**26**:210-20.
40
41
42 45 Vallerand IA, Lewinson RT. Efficacy and adverse events of oral isotretinoin for acne: a
43
44 systematic review. 2017;
45
46
47 46 Huang YC, Cheng YC. Isotretinoin treatment for acne and risk of depression: A
48
49 systematic review and meta-analysis. *J Am Acad Dermatol* 2017;**76**:1068-76.e9.
50
51
52 47 Crandall J, Sakai Y, Zhang J, et al. 13-cis-retinoic acid suppresses hippocampal cell
53
54 division and hippocampal-dependent learning in mice. *Proc Natl Acad Sci U S A*
55
56
57
58
59
60

- 1
2
3
4 2004;**101**:5111-6.
5
6 48 Bremner JD, Fani N, Ashraf A, et al. Functional brain imaging alterations in acne
7
8 patients treated with isotretinoin. *Am J Psychiatry* 2005;**162**:983-91.
9
10
11 49 O'Reilly KC, Trent S, Bailey SJ, et al. 13-cis-Retinoic acid alters intracellular serotonin,
12
13 increases 5-HT1A receptor, and serotonin reuptake transporter levels in vitro. *Exp Biol*
14
15 *Med (Maywood)* 2007;**232**:1195-203.
16
17
18 50 Misery L. Consequences of psychological distress in adolescents with acne. *J Invest*
19
20 *Dermatol* 2011;**131**:290-2.
21
22
23 51 Aktan S, Ozmen E, Sanli B. Anxiety, depression, and nature of acne vulgaris in
24
25 adolescents. *Int J Dermatol* 2000;**39**:354-7.
26
27
28 52 Yang YC, Tu HP, Hong CH. Female gender and acne disease are jointly and
29
30 independently associated with the risk of major depression and suicide: a national
31
32 population-based study. *BioMed Research International* 2014;**2014**:504279.
33
34
35 53 Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and
36
37 psychological morbidity in mid-adolescence: a community-based study. *Br J Dermatol*
38
39 2001;**145**:274-9.
40
41
42
43 54 Thiboutot D, Dreno B, Layton A. Acne counseling to improve adherence. *Cutis*
44
45 2008;**81**:81-6.
46
47
48 55 Hansen TJ, Lucking S, Miller JJ, et al. Standardized laboratory monitoring with use of
49
50 isotretinoin in acne. *J Am Acad Dermatol* 2016;**75**:323-8.
51
52
53
54
55
56
57
58
59
60

Table 1. Characteristics of included studies

Author (year)	Region	Design	Isotretinoin users	Mean/Median age (year)	Female (%)	Acne severity	Comparison groups	Dose	Treatment duration	Depression assessment
Kellett et al. (1999)	UK	Prospective	34	24	44	NA	Before after	vs. 1.0 mg/(kg · d)	4 months	HADS-D
Bick et al. (2000) a	Canada	Retrospective	7195	<30 (75%)	47	NA	Before after	vs. 40 mg (86%)	3–6 months (62%)	ICD code
Bick et al. (2000) b	UK	Retrospective	340	<30 (78%)	42	NA	Before after	vs. 20 mg (75%)	1–2 months (81%)	ICD code
Ng et al. (2002)	Australia	Prospective	174	20	41	Moderate to severe	Before after	vs. 0.8–1.0 mg/(kg · d)	6 months	BDI
Ferahbas et al. (2004)	Turkey	Prospective	23	20	43	Severe	Before after	vs. 0.5–1.0 mg/(kg · d)	4 months	MADRS
Kellett et al. (2005)	UK	Prospective	33	25	36	NA	Before after	vs. 1.0 mg/(kg · d)	4 months	BDI
Kaymak et al. (2006)	Turkey	Prospective	24	100	58	Moderate	Before after	vs. 0.75–1.0 mg/(kg · d)	5–7 months	HRS
Chia et al. (2005)	USA	Prospective	59	12–19	25	Moderate to severe	Before after	vs. 1.0 mg/(kg · d)	3–4 months	CES-D
Azoulay et al. (2008)	Canada	Retrospective	126	28	53	NA	Users nonusers	vs. NA	5 months	ICD code
Kaymak et al. (2009)	Turkey	Prospective	37	21	69	Mild to severe	Before after	vs. 0.5–0.8 mg/(kg · d)	> 5 months	BDI, HADS-D
Pozdag et al. (2009)	Turkey	Prospective	50	20	52	Moderate to severe	Before after	vs. 1.0 mg/(kg · d)	4 months	BDI

1												
2												
3												
4												
5												
6	Rehn et al. (2009)	Finland	Prospective	126	20	0	Moderate	Before	vs.	0.5 mg/(kg · d)	3 months	BDI
7							to severe	after				
8												
9	Simic et al. (2009)	Bosnia and Herzegovina	Prospective	85	19	34	Moderate	Isotretinoin		1.0 mg/(kg · d)	2 months	BDI
10							to severe	vs. vitamin C				
11												
12												
13	McGrath et al. (2010)	UK	Prospective	65	20	31	Mean	Before	vs.	0.5–1.0 mg/(kg · d)	3 months	CES-D
14							AGS	after				
15							score 3.3					
16												
17	Ergun et al. (2012)	Turkey	Prospective	65	22	73	Severe or	Before	vs.	0.5–1.0 mg/(kg · d)	≈ 5 months	HADS-D
18							resistant	after				
19												
20	Ormerod et al. (2012)	UK	Prospective	16	22	25	Severe	Before	vs.	0.5–1.0 mg/(kg · d)	3–6 months	BDI
21								after				
22												
23	Yesilova et al. (2012)	Turkey	Prospective	43	23	70	Mild to	Before	vs.	0.5–1.0 mg/(kg · d)	6 months	HADS-D
24							severe	after				
25												
26	Marron et al. (2013)	Spain	Prospective	346	21	59	Moderate	Before	vs.	Total: 120 mg/kg	7 months	HADS-D
27								after				
28	Fakour et al. (2014)	Iran	Prospective	98	22	61	Severe	Before	vs.	0.5 mg/(kg · d)	4 months	BDI
29								after				
30	Gnanaraj et al. (2015)	India	Prospective	143	21	34	Moderate	Before	vs.	0.5 mg/(kg · d)	3 months	HRS
31							to severe	after				
32												
33	Suarez et al. (2016)	Venezuela	Prospective	36	21	44	Severe	Before	vs.	30 mg/d	3 months	ZDS
34							(25%)	after				

AGS, acne grading scale; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; ICD, International Classification of Diseases; MADRS, Montgomery–Asberg depression rating scale; NA, not available; ZDS, Zung self-rating depression scale.

Table 2. Subgroup analysis for studies presenting depressive symptom scores after isotretinoin compared with the baseline

Subgroups	Number of cohorts	SMD (95% CI)	<i>P</i> value	<i>I</i> ² (<i>P</i> value)
Region				
Europe	14	-0.35 (-0.51 to -0.19)	<0.05	46.3% (<0.05)
Asia	3	-0.18 (-0.81 to 0.45)	0.57	94.4% (<0.05)
North America	1	-0.23 (-0.59 to 0.13)	0.21	–
Africa	1	-0.74 (-1.22 to -0.26)	<0.05	–
Depression scale				
BDI	10	0.10 (-0.12 to 0.32)	0.38	65.2% (<0.05)
HADS-D	4	0.57 (0.31 to 0.83)	<0.05	27.2% (0.25)
CES-D	2	0.27 (0.02 to 0.52)	<0.05	0% (0.78)
HRS	2	0.55 (-0.46 to 1.56)	0.29	96.6% (<0.05)
MADRS	1	0.33 (-0.25 to 0.91)	0.27	–
ZDS	1	0.74 (0.26 to 1.22)	<0.05	–
Sample size				
<50	9	-0.38 (-0.65 to -0.12)	<0.05	64.0% (<0.05)
≥50	11	-0.29 (-0.54 to -0.04)	<0.05	83.1% (<0.05)
Percentage of female patients				
<50	12	-0.32 (-0.55 to -0.09)	<0.05	76.8% (<0.05)
≥50	8	-0.34 (-0.04 to -0.64)	<0.05	78.4% (<0.05)

BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; MADRS, Montgomery–Asberg depression rating scale; SMD, standardized mean difference; ZDS, Zung self-rating depression scale.

1
2
3
4 **Figure legends:**
5

6 **Figure. 1.** Study selection process.
7

8 **Figure. 2.** Forest plot showing the standardized mean difference for the comparison of
9 depression symptom scores before and after isotretinoin treatment in acne patients.
10
11

12 **Figure. 3.** Funnel plot of studies comparing depression symptom scores before and after
13 isotretinoin treatment in acne patients.
14
15

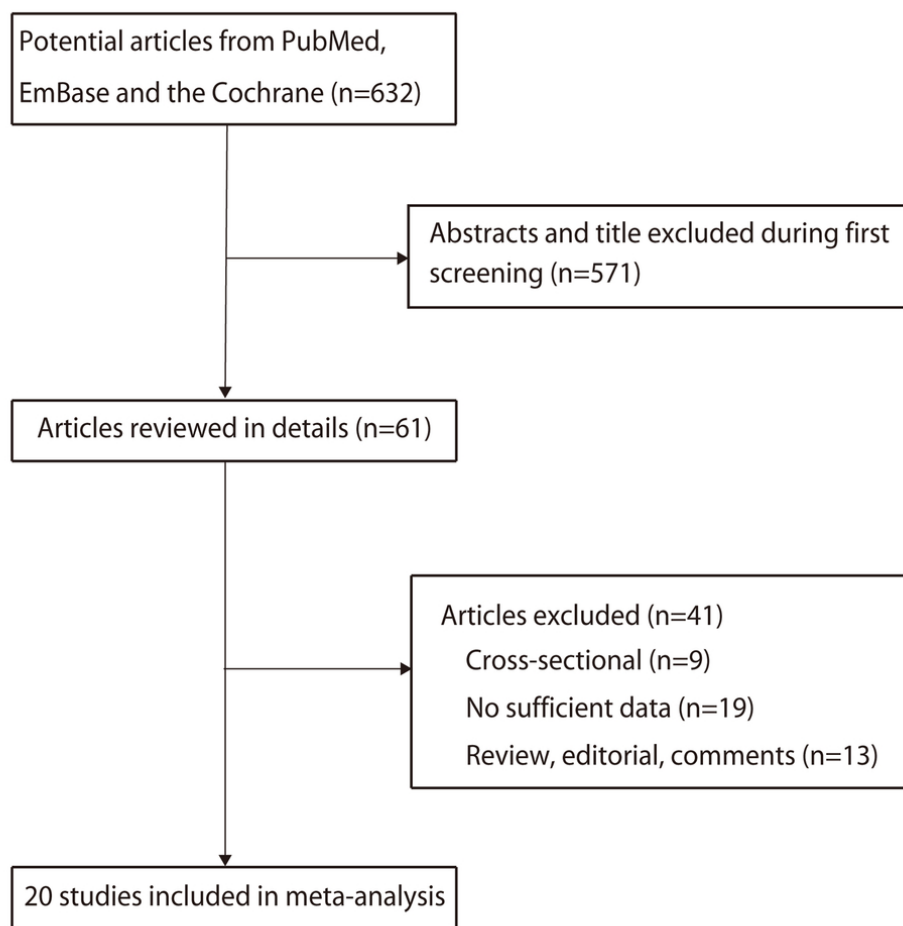
16 **Figure. 4.** Forest plot showing the weighted mean difference for the comparison of BDI
17 scores before and after isotretinoin treatment in acne patients.
18
19

20 **Figure. 5.** Forest plot showing the association between isotretinoin treatment and
21 depression in acne patients.
22
23

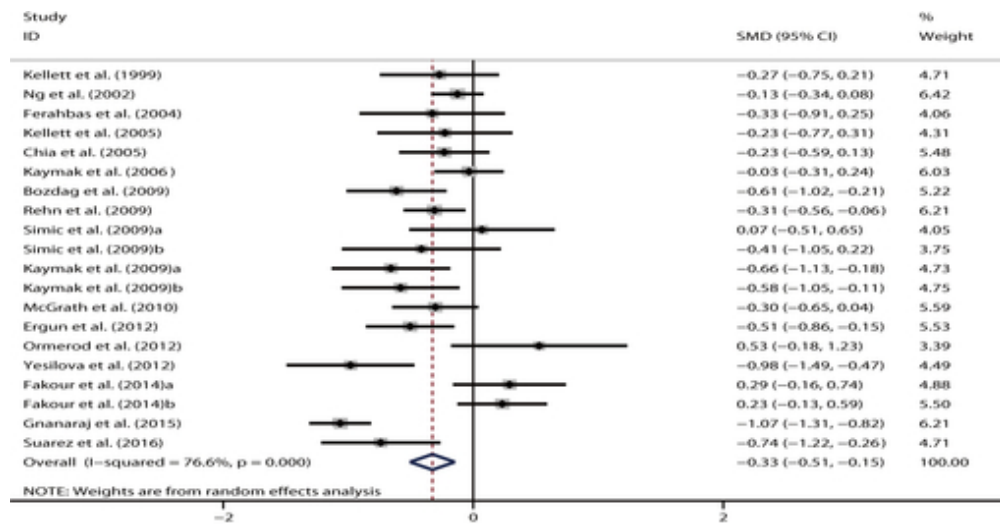
24 **Figure. 6.** Funnel plot of showing the association between isotretinoin treatment and
25 depression in acne patients.
26
27
28

29
30
31
32
33
34
35
36 **Legends for supporting information**
37

38
39 **Supplemental Table1.** Newcastle–Ottawa scale for quality assessment of included studies
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

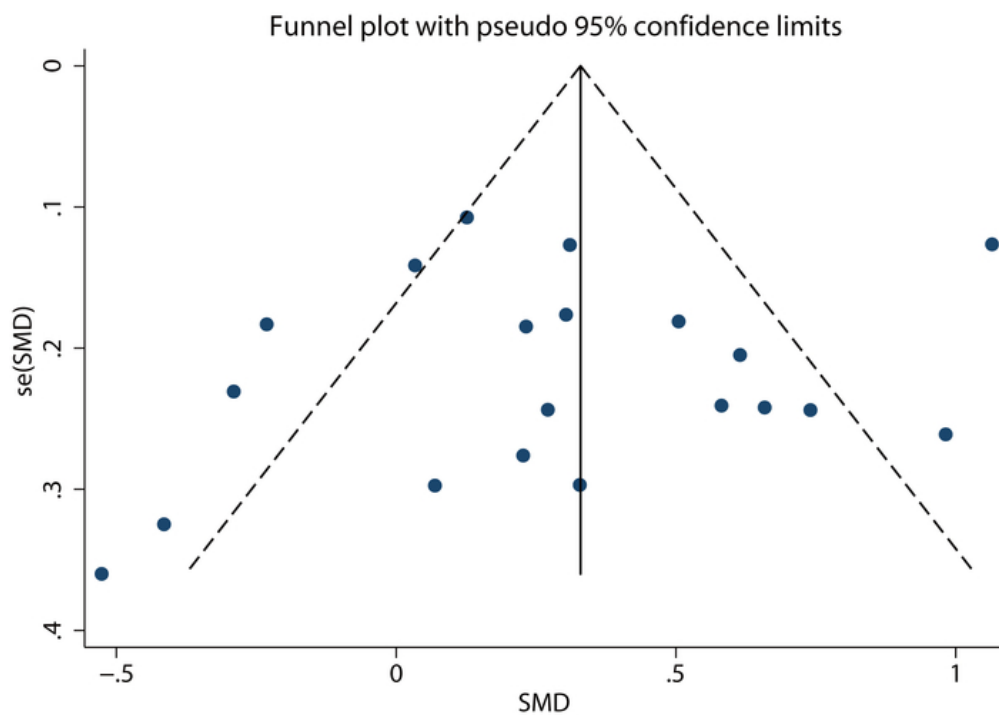


83x83mm (300 x 300 DPI)



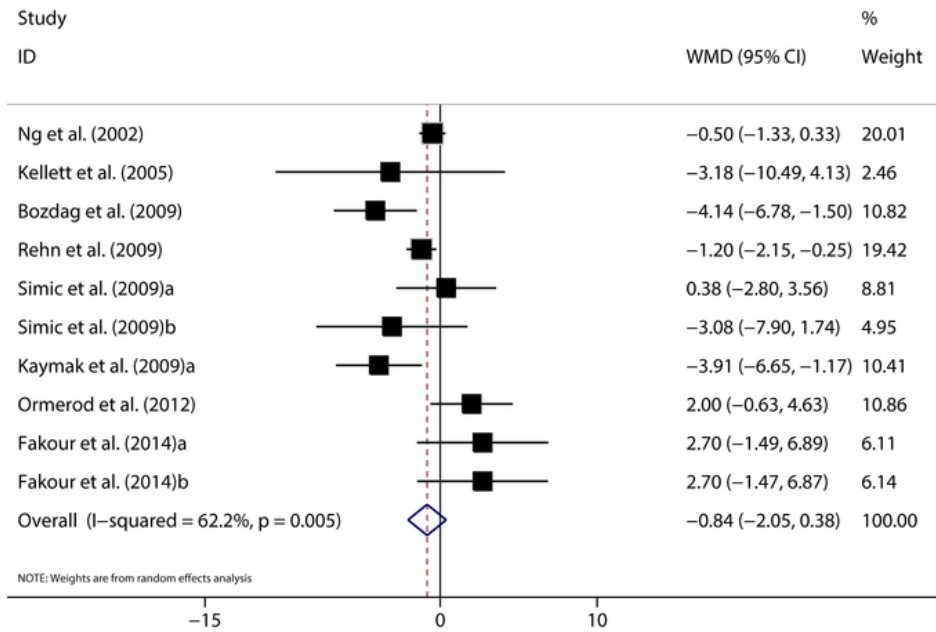
43x22mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

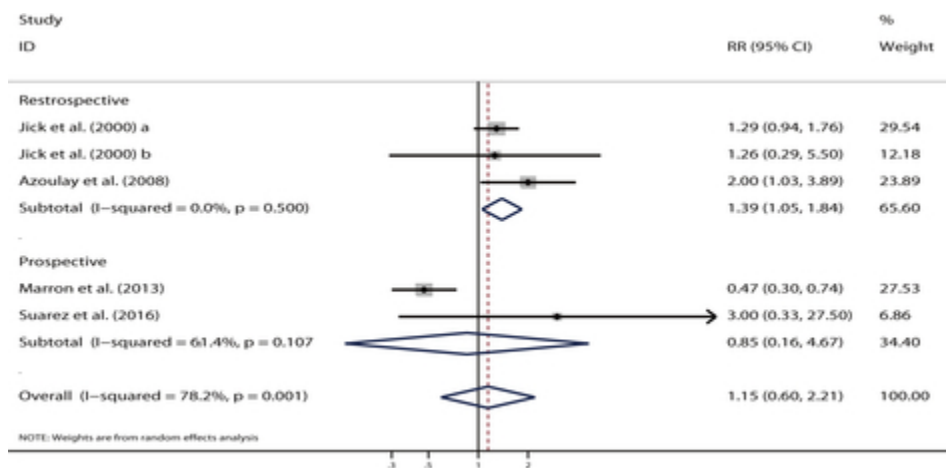


59x41mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

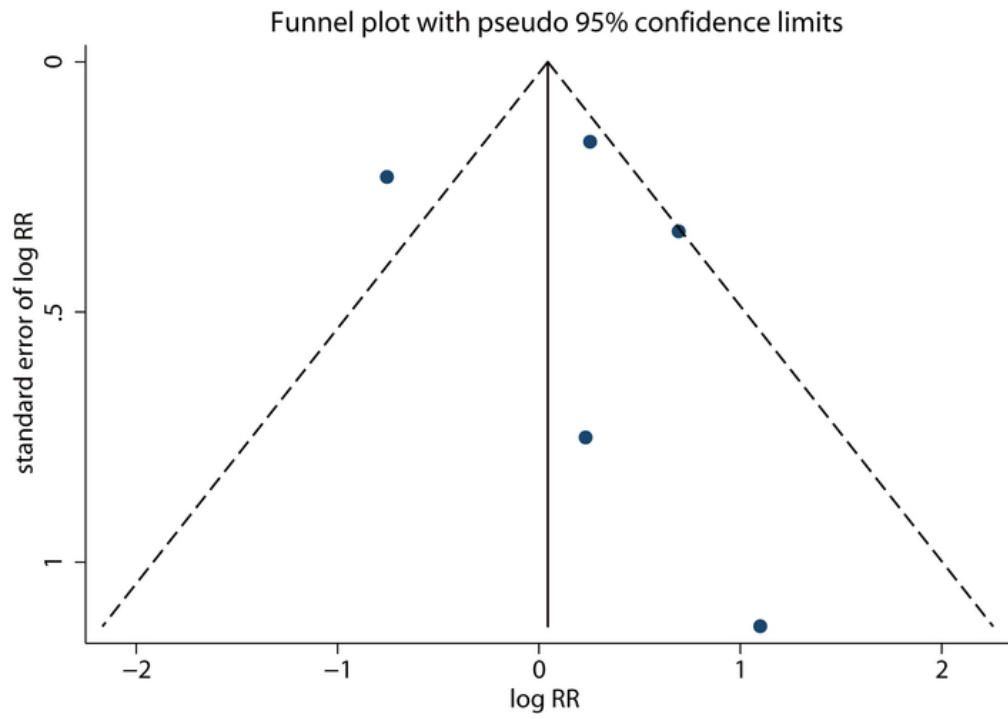


61x44mm (300 x 300 DPI)



40x19mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



59x41mm (300 x 300 DPI)

Supplementary Table 1 Newcastle–Ottawa scale for quality assessment of included studies

Study	Selection	Comparability	Outcome
Kellett et al. (1999)	****	*	***
Jick et al. (2000) a	****	**	**
Jick et al. (2000) b	****	**	**
Ng et al. (2002)	****	*	***
Ferahbas et al. (2004)	****	*	***
Kellett et al. (2005)	****	*	***
Kaymak et al. (2006)	****	*	***
Chia et al. (2005)	***	*	***
Azoulay et al. (2008)	****	**	**
Kaymak et al. (2009)	****	*	***
Bozdog et al. (2009)	****	*	***
Rehn et al. (2009)	***	*	***
Simic et al. (2009)	****	*	***
McGrath et al. (2010)	****	*	***
Ergun et al. (2012)	****	*	***
Ormerod et al. (2012)	***	*	***
Yesilova et al. (2012)	****	*	***
Marron et al. (2013)	****	*	***
Fakour et al. (2014)	****	*	***
Gnanaraj et al. (2015)	****	*	***
Suarez et al. (2016)	****	*	***



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021549.R1
Article Type:	Research
Date Submitted by the Author:	25-May-2018
Complete List of Authors:	Li, Changqiang ; the Affiliated Hospital of Southwest Medical University, Department of Dermatology Chen, Jianmei ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Wang, Wo ; University-Town Hospital of Chongqing Medical University, Mental Health Center Ai, Ming ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Zhang, Qi ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Kuang, Li
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Dermatology
Keywords:	Acne < DERMATOLOGY, Depression & mood disorders < PSYCHIATRY, ORAL MEDICINE

SCHOLARONE™
Manuscripts

1
2
3 **Use of isotretinoin and risk of depression in patients with acne: a systematic review and**
4
5 **meta-analysis**
6

7
8 Changqiang Li², Jianmei Chen¹, Wo Wang³, Ming Ai¹, Qi Zhang¹, Li Kuang^{1*}
9

10
11 ¹Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical University,
12
13 Chongqing 400016, China
14

15
16 ²Department of Dermatology, the Affiliated Hospital of Southwest Medical University,
17
18 Luzhou646000, China
19

20
21 ³Mental Health Center, University-Town Hospital of Chongqing Medical University,
22
23 Chongqing 401331, China
24

25
26
27
28 ***Corresponding author:**
29

30 Li Kuang
31

32
33 Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical University,
34
35 Chongqing 400016, China
36

37
38 Tel: +86-13908379733
39

40
41 Fax: +86-21-64085875
42

43
44 Email: kuangli0308@163.com
45
46

47 **Running title:** Isotretinoin and risk of depression in patients with acne
48
49
50
51
52
53
54
55
56
57

ABSTRACT

Objective: This study aimed to investigate the association between the use of isotretinoin and the risk of depression in patients with acne.

Design: This was a meta-analysis in which the standardized mean difference (SMD) and the relative risk (RR) were used for data synthesis employed the random-effects model.

Setting: Studies were identified via electronic searches of PubMed, Embase, and the Cochrane Library up to December 28, 2017.

Participants: Patients with acne.

Interventions: Studies comparing isotretinoin with other interventions in patients with acne were included.

Results: Twenty studies were selected. The analysis of 17 studies showed a significant association of the use of isotretinoin with improved symptoms compared with the baseline before treatment [SMD = -0.33, 95% confidence interval (CI) -0.51 to -0.15, $P < 0.05$; $I^2 = 76.6\%$, $P < 0.05$]. Four studies were related to the analysis of the risk of depression. The pooled data indicated no association of the use of isotretinoin with the risk of depressive disorders (RR = 1.15, 95% CI 0.60–2.21, $P = 0.14$). The association of the use of isotretinoin with the risk of depressive disorders was statistically significant on pooling retrospective studies (RR = 1.39, 95% CI 1.05–1.84, $P = 0.02$), but this association was not evident on pooling prospective studies (RR = 0.85, 95% CI 0.60–2.21, $P = 0.86$).

1
2
3
4 **Conclusions:** This study suggested an association of the use of isotretinoin in patients with
5
6 acne with significantly improved depression symptoms. Future randomized controlled trials
7
8 are needed to verify the present findings.
9

10 11 12 13 **Strengths and limitations of this study**

- 14
15
16 1. Most included studies were prospectively designed, and the quality of included studies
17
18 was largely moderate to high.
19
20
21 2. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses.
22
23
24 3. The small sample sizes of some included studies might have limited the statistical power
25
26 and increased the chance of missing small effects.
27
28
29 4. No randomized controlled trial was available so far, which was a major drawback for
30
31 studies on this topic.
32
33
34 5. The treatment duration, drug dose, and depression scale varied between different studies.
35
36
37
38

39 **Key words:** acne; depression; isotretinoin; meta-analysis
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit of the face, neck, chest, and back¹. As a pleomorphic skin disease, it may present as noninflammatory lesions (open and closed comedones) or inflammatory lesions (papules, pustules, or nodules)². It is the most common skin disease around the world, with an estimated prevalence of 70%–87%³. The economic burden of acne is substantial. The cost is estimated to exceed \$1 billion per year in the United States for direct acne therapy, with \$100 million spent on various acne products⁴. Acne vulgaris may cause cosmetic defects and significantly impact the quality of life⁵. It may provoke a wide range of mental problems, including depression, anxiety, poor self-esteem, social phobia, and even suicidal attempts⁶.

The optimal treatment approach depends on the morphology and severity of acne. Mild cases are suggested to be treated with topical retinoids. For moderate cases, systemic drugs are always needed, including oral antibiotics, hormonal therapy, and oral retinoids. However, for severe or resistant moderate acne, isotretinoin is the treatment of choice^{1,2,4,7}. Isotretinoin is a vitamin A-derivative 13-*cis*-retinoic acid, which is the most effective therapy for acne to date. It targets all four processes during acne development, including normalization of follicular desquamation, reduction of sebaceous gland activity, inhibition of the proliferation of *Propionibacterium acnes*, and anti-inflammatory effects^{2,7,8}. The meta-analysis suggested that isotretinoin cured around 85% of patients after an average treatment course of 4 months⁹.

1
2
3 Depressive disorders are highly prevalent in the Western world. The lifetime prevalence of
4
5
6 major depressive disorders in the United States and Western Europe is around 13%–16%¹⁰.
7
8
9 The frequency of depressive disorders during the use of isotretinoin varies from 1% to 11%
10
11¹¹. Theoretically, effective treatment may lead to an improvement in depressive symptoms
12
13 of patients with acne. However, the use of systemic isotretinoin itself may potentially
14
15 increase the risk of depression¹². Experimental studies showed that isotretinoin could affect
16
17 the central nervous system and was involved in the pathogenesis of depression¹³. However,
18
19 some researchers disputed that the risk was extremely small and might be influenced by the
20
21 background risk or nondrug confounding factors¹². The evidence for this controversy
22
23 remained incomplete and unclear. Therefore, this systematic review and meta-analysis was
24
25 performed to explore the association between the use of isotretinoin and the risk of
26
27 depression among patients with acne. Further, whether this relationship differed in patients
28
29 with specific characteristics was also explored.
30
31
32
33
34
35
36
37
38
39

40 **METHODS**

41 **Literature search**

42
43 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was
44
45 followed to conduct this meta-analysis¹⁴. A literature search up to December 28, 2017, was
46
47 performed using PubMed, Embase, and the Cochrane Library. The following groups of
48
49 keywords were used in the search: (“depression” OR “depressive”) AND “acne” AND
50
51 “isotretinoin.” The details of searching strategy in PubMed are presented in Supplemental 1.
52
53
54
55
56

1
2
3 Also, a manual search of references listed in included studies and published reviews were
4
5
6 also performed to search for potentially eligible studies. The language was restricted to
7
8
9 English.

10 11 **Selection criteria**

12
13 Studies were included if they fulfilled the following criteria: (1) being randomized
14
15 controlled trial (RCT), prospective or retrospective study, nested case-control study, or
16
17 population-based case-control study; (2) comparing the outcomes before and after the use
18
19 of isotretinoin in patients with acne; or comparing isotretinoin with other treatment
20
21 regimens in patients with acne; (3) presenting the change in depressive symptoms measured
22
23 using a continuous depression scale¹⁵; or reporting the number of depressive patients before
24
25 and after the use of isotretinoin; or directly presenting the relative risk (RR), odds ratio
26
27 (OR), or hazard ratio (HR) between the use of isotretinoin and the risk of depression.
28
29
30
31
32
33

34 **Data extraction and quality assessment**

35
36 Two authors independently assessed the titles and abstracts for eligibility and extracted data
37
38 in standardized electronic tables. The following data were extracted from included studies:
39
40 publication year, author, study design, sample size, participant sex and age, severity of acne,
41
42 compared groups, dose and duration of isotretinoin, and depression assessment tool. The
43
44 quality of included studies was assessed using the 9-star Newcastle-Ottawa Scale. This
45
46 scale evaluated the study quality based on three parameters: selection, comparability, and
47
48 exposure (case-control study) or outcome (cohort study). A maximum of 4 points was
49
50 assigned for the item of selection, 2 points for comparability, and 3 points for
51
52
53
54
55
56
57
58
59
60

1
2
3 exposure/outcome ¹⁶. Studies were deemed as high quality for a score of 8–9, moderate
4 quality for a score of 6–7, and low quality for a score ≤ 5 .
5
6
7

8 **Statistical analysis**

9
10 The continuous outcome of interest was the alteration in depressive symptoms assessed
11 using a continuous depression scale after the use of isotretinoin. For the continuous
12 parameter of depression score, the means and standard differences (SD) of the scores were
13 extracted. The standard mean difference (SMD) was used as the outcome measure. The
14 SMD was a unitless effect size estimate, which was the mean difference in the depression
15 score between the compared groups divided by the pooled SD of the distribution of the
16 score used in the study. The conversion of median (range/interquartile range) to mean \pm SD
17 was done by a previously proposed method ¹⁷. The binary outcome of interest was the
18 number of participants whose conditions were regarded as depression. RR and its
19 corresponding 95% confidence interval (CI) were used as the outcome measure. HR was
20 regarded as equivalent to RR in cohort studies. Given the overall low incidence of
21 depression among the general population, OR was assumed to be an accurate estimate of
22 RR. It was preferred to use the effect measures that reflected the greatest degree control for
23 confounding factors. Both adjusted and crude data were analyzed. When data on different
24 subgroups were reported by the same cohort, they were first pooled using the fixed-effects
25 model. As the random-effects model was more robust than the fixed-effects model, the
26 DerSimonian–Laird random-effects model was used to calculate the overall effect estimates
27 for the association between the use of isotretinoin and the risk of depression ¹⁸. The
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 heterogeneity was evaluated using the Cochran Q test and the I^2 statistic. Heterogeneity
4 was considered low, moderate, or high for $I^2 < 25\%$, $25\%–50\%$, and $>50\%$, respectively^{19,20}.
5
6 Subgroup analyses were conducted based on the following confounders: region, study
7
8 design, sample size, female percentage, and depression scale. Furthermore, meta-regression
9
10 analyses were performed for the continuous confounders of sample size and female
11
12 percentage. A sensitivity analysis was conducted by excluding a single study at a time. Also,
13
14 a sensitivity analysis was conducted using the weighted mean difference (WMD) as the
15
16 effect estimate for studies employing the same depression symptom scale. The publication
17
18 bias was visually assessed by constructing a funnel plot and statistically assessed using the
19
20 Begg's and Egger's regression asymmetry tests^{21,22}. All statistical analyses were conducted
21
22 using the software Stata 12.0 (StataCorp, TX, USA). A *P* value less than 0.05 was
23
24 considered statistically significant.
25
26
27
28
29
30
31
32

33 34 **Patient and public involvement statement**

35
36 Patients and the public were not involved
37
38
39
40
41

42 **RESULTS**

43 44 **Study selection**

45
46 A total of 632 records were retrieved from the electronic search, including 145 studies from
47
48 PubMed, 469 records from Embase, and 18 records from the Cochrane Library. After
49
50 screening by titles and abstracts, 571 studies were excluded for the following reasons:
51
52 reviews, editorials, case reports, or irrelevant studies, leaving 61 studies for full-text review.
53
54
55
56
57

1
2
3
4 Nine cross-sectional studies, 19 studies without sufficient data, and 13 review, editorial, or
5
6 comments were excluded. Finally, 20 studies were pooled into the meta-analysis²³⁻⁴³. A
7
8 flow diagram of the study selection process is depicted in Figure 1.
9

10 11 **Study characteristics**

12
13 The characteristics of the included 20 studies are shown in Table 1. Jick et al. reported two
14
15 independent cohorts²⁴, which were analyzed separately. Except for two retrospective
16
17 studies identifying depressive patients using the International Classification of Diseases
18
19 code^{24, 31}, other studies were prospectively designed, and depression was assessed using
20
21 depression symptom scales. The number of participants using isotretinoin ranged from 16 to
22
23 7195. The enrolled patients with acne were distributed around the world, including 14
24
25 cohorts from Europe, 3 from North America, 3 from Asia, and 1 from Africa. The
26
27 percentage of female patients ranged from 0% to 73%. Most studies compared data before
28
29 and after the use of isotretinoin, except for two studies. Simic et al. compared isotretinoin
30
31 with vitamin C³⁵. Azoulay et al. compared isotretinoin users with nonusers³¹. Most studies
32
33 prescribed isotretinoin for moderate-to-severe acne. The dose of isotretinoin ranged largely
34
35 from 0.5 to 1.0 mg/(kg · d). The duration of the use of isotretinoin ranged from around 1
36
37 month to about half a year. The quality of included studies is shown in Supplemental 2.
38
39 Most studies had satisfactorily high quality. The least satisfactory item was the adjustment
40
41 of the confounding factors.
42
43
44
45
46
47
48
49
50

51 52 **Change in depression symptom scores after treatment**

1
2
3
4 Seventeen studies reported the depression symptom scores before and after the use of
5
6 isotretinoin. All studies were prospectively designed. Simic et al. (2009) presented data for
7
8 moderate and severe acne³⁵. Fakour et al. showed data for males and females separately³⁷.
9
10
11 Kaymak et al. reported depression scores measured using Beck Depression Inventory (BDI)
12
13 and hospital anxiety and depression scale-depression (HADS-D) scales³³. These subgroup
14
15 data were all pooled into the overall analysis. Compared with the baseline condition before
16
17 therapy, the use of isotretinoin was associated with a significant improvement in depressive
18
19 symptoms (SMD = -0.33, 95% CI -0.51 to -0.15, $P < 0.05$) (Fig. 2). Highly significant
20
21 heterogeneity was revealed ($I^2 = 76.6%$, $P < 0.05$).
22
23
24

25
26 In the sensitivity analysis, the overall effect was not substantially altered when excluding
27
28 any single study. In the meta-regression analysis, the number of included participants ($P =$
29
30 0.995) and the female proportion ($P = 0.56$) did not account for the source of heterogeneity.
31
32
33 Data on subgroup analyses are shown in Table 2. The pooled effect estimate remained
34
35 significant for 14 European studies (SMD = -0.35, 95% CI -0.51 to -0.19, $P < 0.05$), with
36
37 moderate heterogeneity ($I^2 = 46.3%$). However, the analysis of three Asian studies did not
38
39 show significant results (SMD = -0.18, 95% CI -0.81 to 0.45, $P = 0.57$; $I^2 = 94.4%$). The
40
41 use of isotretinoin had no significant effect on depressive symptoms in North America
42
43 (SMD = -0.23, 95% CI -0.59 to 0.13; $P = 0.21$), while it was associated with improved
44
45 depressive symptoms in Africa (SMD = -0.74, 95% CI -1.22 to -0.26, $P < 0.05$). The
46
47 pooled results remained significant for studies using HADS-D (SMD = -0.57, 95% CI
48
49 -0.83 to -0.31, $P < 0.25$; $I^2 = 27.2%$), and those using the Center for Epidemiological
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Studies Depression scale (CES-D) (SMD = -0.27, 95% CI -0.52 to -0.02, $P < 0.05$; $I^2 = 0\%$). However, the pooled effect turned to be nonsignificant for studies using the BDI scale (SMD = -0.15, 95% CI -0.36 to 0.06, $P = 0.17$; $I^2 = 62.4\%$) and those using the Hamilton Rating Scale (HRS) (SMD = -0.55, 95% CI -1.56 to 0.46, $P = 0.29$; $I^2 = 96.6\%$). The pooled effects were significant for both studies with a smaller sample size (SMD = -0.38, 95% CI -0.65 to -0.12, $P < 0.05$) and those with a larger sample size (SMD = -0.29, 95% CI -0.54 to -0.04, $P < 0.05$). The results for different proportions of females did not show a significant difference. The funnel plot appeared to be symmetrical (Fig. 3). No publication bias was revealed using the Egger's test ($P = 0.76$) or the Begg's test ($P = 0.87$).

Also, the sensitivity analysis was performed by pooling the WMD for studies using the same scale. The pooled results were nonsignificant for studies using the BDI scale (WMD = -0.84, 95% CI -2.05 to 0.38, $P = 0.18$; $I^2 = 62.2\%$, $P < 0.05$) (Fig. 4) and those using HRS (WMD = -1.91, 95% CI -5.44 to 1.63, $P = 0.29$; $I^2 = 97.3\%$, $P < 0.05$). In contrast, the pooled WMDs were significant for studies using HADS-D (WMD = -2.06, 95% CI -3.42 to -0.70, $P < 0.05$; $I^2 = 66.0\%$, $P < 0.05$) and those using CES-D (WMD = -1.88, 95% CI -3.64 to -0.11, $P < 0.05$; $I^2 = 0\%$, $P = 0.63$).

Use of isotretinoin and risk of depression

Two retrospective studies showed the adjusted RR for the association between the use of isotretinoin and the risk of depression^{24, 31}. Jick et al. presented data for two independent cohorts. The overall result of three cohorts showed that the use of isotretinoin was associated with an increased risk of depression (RR = 1.39, 95% CI 1.05–1.84, $P = 0.02$;

1
2
3
4 Fig. 5), and no significant heterogeneity was shown ($I^2 = 0.0\%$, $P = 0.50$). However, no
5
6 significant difference was noted in the relationship between isotretinoin use and the risk of
7
8 depression on pooling two prospective studies (RR = 0.85, 95% CI 0.60–2.21, $P = 0.86$; Fig.
9
10 5), and a substantial heterogeneity was observed ($I^2 = 61.4\%$, $P = 0.11$). The funnel plot
11
12 appeared to be symmetrical (Fig. 6), and the Egger's test ($P = 0.76$) or the Begg's test ($P =$
13
14 1.00) suggested no evidence of potential publication bias.
15
16
17
18
19
20

21 DISCUSSION

22
23
24 The risk of depression associated with the use of isotretinoin in patients with acne has been
25
26 a major concern for a long time. Previous data showed conflicting and inconsistent results.
27
28

29 This meta-analysis assessed the association between the use of isotretinoin and the risk of
30
31 depression. It had several strengths as follows. A comprehensive database search of
32
33 worldwide cohorts was conducted, enrolling a large number of participants. The quality of
34
35 included studies was largely moderate to high. Most included studies were prospectively
36
37 designed. The association was investigated from several aspects. The heterogeneity was
38
39 explored by sensitivity, subgroup, and meta-regression analyses. The present findings
40
41 showed that isotretinoin improved in depressive symptoms in patients with acne. The
42
43 benefit remained marked for studies using HADS-D and CES-D. In risk assessment, the
44
45 summary RR showed that the use of isotretinoin was associated with an increased risk of
46
47 depression in patients with acne on pooling retrospective studies, while this significant
48
49 difference was not observed on pooling prospective studies.
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 Two previous systematic reviews on this topic were identified^{13,44}. They showed conflicting
5
6 results, and hence the association between isotretinoin use and depression remained
7
8 controversial. Further, although comprehensive scenarios were presented, data synthesis to
9
10 obtain pooled results could not be conducted. Vallerand conducted a systematic review based
11
12 on 11 trials to evaluate the efficacy and safety of oral isotretinoin for acne. Oral isotretinoin
13
14 significantly reduced the counts of acne lesions but increased the frequency of psychiatric
15
16 adverse events (depressed mood, fatigue, hallucination, insomnia, and lethargy; 32 vs 19).
17
18 However, this study did not provide the result by data synthesis⁴⁵. Further, Huang et al
19
20 conducted a meta-analysis based on 31 studies and suggested that the use of isotretinoin did
21
22 not affect the incidence of depression. Further, they showed that the treatment of acne could
23
24 ameliorate depressive symptoms. However, the study summarized the investigated outcomes
25
26 using the depression assessment tool. Whether these relationships differed according to the
27
28 region, study design, sample size, and the female percentage was not illustrated⁴⁶. Therefore,
29
30 the present study was conducted to evaluate any potential impact of the use of isotretinoin on
31
32 depression incidence and change in the depression score.
33
34
35
36
37
38
39
40

41
42 The concern for negative mood arose from a series of experimental studies. Oral isotretinoin
43
44 significantly suppressed cell division in the hippocampus and severely disrupted the
45
46 learning capacity of mice⁴⁷. Bremner et al. found that the use of isotretinoin, but not
47
48 antibiotics, was associated with decreased brain metabolism in the orbitofrontal cortex,
49
50 which was known to mediate depression symptoms⁴⁸. O'Reilly et al. proved that
51
52 isotretinoin altered intracellular serotonin level and increased 5-HT1A receptor and
53
54
55
56
57
58
59
60

1
2
3 serotonin reuptake transporter levels *in vitro*⁴⁹. Thus, theoretically, isotretinoin itself might
4
5
6 cause depressive disorders. However, the potentially increased risk of depression could be
7
8
9 compensated by the beneficial effects of isotretinoin on patients with acne. Most patients
10
11 with acne were worried about their appearances, which might lead to a series of
12
13 psychological disorders. It was inferred that the improvement in depression symptoms after
14
15 the use of isotretinoin might be attributed to the treatment success. Also, isotretinoin had a
16
17 gradual effect on mood over time, which was not an acute event⁵⁰.

21 Of note, the controversy over this topic was complicated by various confounding
22
23 psychosocial and clinical factors. Aktan et al. suggested that adolescent girls were more
24
25 vulnerable to the negative psychological effects of acne compared with boys⁵¹. Women
26
27 with acne were significantly more embarrassed about their skin disease compared with
28
29 males. A large database study showed that female gender and acne could jointly increase
30
31 the risk of depression⁵². However, the role of gender was not revealed in meta-regression
32
33 and subgroup analyses. Acne itself can exert different impacts on individual patients. The
34
35 lack of knowledge, especially about prognosis, may be a source of depression^{24, 53}.
36
37 Approximately one fifth of patients with acne suffered from psychiatric disorders³³. Better
38
39 health education and care are important components for treating patients with acne. They
40
41 help eliminate the patients' misconceptions about the disease and unrealistic treatment
42
43 expectations⁵⁴. The psychological interventions may vary between different clinical
44
45 settings and lead to a bias in the effect of isotretinoin. Besides, data on the efficacy or side
46
47 effect of the use of isotretinoin were insufficient in most included studies. Isotretinoin may
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 cause teratogenic toxicity. Contraceptives are recommended for female users of fertile age
5
6 to prevent pregnancy until the completion of the treatment ⁴¹. The levels of blood
7
8 cholesterol and liver enzymes may be abnormal and should be monitored during the
9
10 treatment phase ⁵⁵.

11
12
13 This meta-analysis had several shortcomings. The sample sizes of some included studies
14
15 were still small, which might have limited the statistical power and increased the chance of
16
17 missing small effects. Cohort studies might have a bias caused by participant selection and
18
19 confounding factors. Most studies compared the before- and after-treatment data. Ideally,
20
21 RCTs comparing isotretinoin with placebo or other agents may provide more robust
22
23 findings. However, leaving patients with moderate-to-severe acne without the use of
24
25 isotretinoin may be unfair and even not ethical. However, no RCT was available so far,
26
27 which was a major drawback for studies on this topic. Additionally, the treatment duration,
28
29 drug dose, and depression scale varied between different studies. The acne severity or the
30
31 dose of isotretinoin varied and was not reported by several studies. Patients with severe
32
33 acne or scars or those unresponsive to therapy might have a worse depressive mood.
34
35 However, the analyses for these confounding factors were insufficient in most studies.
36
37
38
39
40
41
42
43
44 Approximately one fifth of patients with acne suffered from psychiatric disorders ³³. Also,
45
46 some studies were sponsored by corporations ²⁴, which might have underestimated the
47
48 incidence of depressive disorders. Finally, although a greater risk of depression was
49
50 associated with the use of isotretinoin on pooling retrospective studies, selection and recall
51
52
53
54
55
56
57
58
59
60

1
2
3 biases might have affected the incidence of depression. Further, these conclusions might be
4
5
6 unreliable because smaller cohorts were included in such subsets.
7

8
9 This meta-analysis showed that patients might have improved depressive symptoms after
10
11 the use of isotretinoin. Further, the use of isotretinoin in patients with acne did not
12
13 contribute to the development of depression. However, the summary results of retrospective
14
15 studies suggested that the use of isotretinoin in patients with acne might increase the risk of
16
17 depression. Future prospective controlled trials are warranted to verify the present findings.
18
19
20
21
22
23

24 **Funding**

25
26 Not applicable.
27
28
29
30

31 **Conflicts of interest statement**

32
33 Not declared.
34
35
36
37
38

39 **Author contributions**

40
41 CQL and LK contributed to conception and design. CQL, JMC, WW, MA, QZ, and LK
42
43 contributed to data acquisition or analysis and interpretation of data. CQL, JMC, WW, MA,
44
45 QZ, and LK were involved in drafting the manuscript or revising it critically for important
46
47 intellectual content. All authors have given final approval of the version to be published.
48
49
50
51
52
53

54 **Data sharing statement**

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

No additional data are available.

For peer review only

REFERENCES

- 1 Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet* 2012;**379**:361-72.
- 2 Katsambas AD, Stefanaki C, Cunliffe WJ. Guidelines for treating acne. *Clin Dermatol* 2004;**22**:439-44.
- 3 Dreno B, Poli F. Epidemiology of acne. *Dermatology* 2003;**206**:7-10.
- 4 James WD. Clinical practice. Acne. *N Engl J Med* 2005;**352**:1463-72.
- 5 Thomas DR. Psychosocial effects of acne. *J Cutan Med Surg* 2004;**8 Suppl 4**:3-5.
- 6 Saitta P, Keehan P, Yousif J, et al. An update on the presence of psychiatric comorbidities in acne patients, Part 2: Depression, anxiety, and suicide. *Cutis* 2011;**88**:92-7.
- 7 Dawson AL, Dellavalle RP. Acne vulgaris. *BMJ* 2013;**346**:f2634.
- 8 Chivot M. Retinoid therapy for acne. A comparative review. *Am J Clin Dermatol* 2005;**6**:13-9.
- 9 Wessels F, Anderson AN, Kropman K. The cost-effectiveness of isotretinoin in the treatment of acne. Part 1. A meta-analysis of effectiveness literature. *S Afr Med J* 1999;**89**:780-4.
- 10 Kurek A, Johanne Peters EM, Sabat R, et al. Depression is a frequent co-morbidity in patients with acne inversa. *J Dtsch Dermatol Ges* 2013;**11**:743-9, 43-50.
- 11 Borovaya A, Olisova O, Ruzicka T, et al. Does isotretinoin therapy of acne cure or cause depression? *Int J Dermatol* 2013;**52**:1040-52.
- 12 Wolverton SE, Harper JC. Important controversies associated with isotretinoin therapy for acne. *Am J Clin Dermatol* 2013;**14**:71-6.

- 1
2
3
4 13 Kontaxakis VP, Skourides D, Ferentinos P, et al. Isotretinoin and psychopathology: a
5
6 review. *Ann Gen Psychiatry* 2009;**8**:2.
7
8
9 14 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews
10
11 and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.
12
13
14 15 Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck
15
16 Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale
17
18 (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale
19
20 (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)*
21
22 2011;**63 Suppl 11**:S454-66.
23
24
25
26 16 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing
27
28 the quality of nonrandomised studies in meta-analyses.
29
30 http://www.ohrica/programs/clinical_epidemiology/oxfordasp
31
32
33
34 17 Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from
35
36 the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*
37
38 2014;**14**:135.
39
40
41
42 18 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*
43
44 1986;**7**:177-88.
45
46
47 19 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses.
48
49 *BMJ* 2003;**327**:557-60.
50
51
52 20 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*
53
54 2002;**21**:1539-58.
55
56
57
58
59
60

- 1
2
3
4 21 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for
5
6 publication bias. *Biometrics* 1994;**50**:1088-101.
7
8
9 22 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple,
10
11 graphical test. *BMJ* 1997;**315**:629-34.
12
13
14 23 Kellett SC, Gawkrödger DJ. The psychological and emotional impact of acne and the
15
16 effect of treatment with isotretinoin. *Br J Dermatol* 1999;**140**:273-82.
17
18
19 24 Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression,
20
21 psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* 2000;**136**:1231-6.
22
23
24 25 Ng CH, Tam MM, Celi E, et al. Prospective study of depressive symptoms and quality of
25
26 life in acne vulgaris patients treated with isotretinoin compared to antibiotic and topical
27
28 therapy. *Australas J Dermatol* 2002;**43**:262-8.
29
30
31 26 Ferahbas A, Turan MT, Esel E, et al. A pilot study evaluating anxiety and depressive
32
33 scores in acne patients treated with isotretinoin. *J Dermatolog Treat* 2004;**15**:153-7.
34
35
36 27 Chia CY, Lane W, Chibnall J, et al. Isotretinoin therapy and mood changes in adolescents
37
38 with moderate to severe acne: a cohort study. *Arch Dermatol* 2005;**141**:557-60.
39
40
41 28 Kellett SC, Gawkrödger DJ. A prospective study of the responsiveness of depression and
42
43 suicidal ideation in acne patients to different phases of isotretinoin therapy. *Eur J*
44
45 *Dermatol* 2005;**15**:484-8.
46
47
48 29 Kaymak Y, Kalay M, Ilter N, et al. Incidence of depression related to isotretinoin
49
50 treatment in 100 acne vulgaris patients. *Psychol Rep* 2006;**99**:897-906.
51
52
53 30 Cohen J, Adams S, Patten S. No association found between patients receiving
54
55
56
57
58
59
60

- 1
2
3 isotretinoin for acne and the development of depression in a Canadian prospective
4
5 cohort. *Can J Clin Pharmacol* 2007;**14**:e227-33.
6
7
- 8
9 31 Azoulay L, Blais L, Koren G, et al. Isotretinoin and the risk of depression in patients
10
11 with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008;**69**:526-32.
12
- 13
14 32 Bozdag KE, Gulseren S, Guven F, et al. Evaluation of depressive symptoms in acne
15
16 patients treated with isotretinoin. *J Dermatolog Treat* 2009;**20**:293-6.
17
- 18
19 33 Kaymak Y, Taner E, Taner Y. Comparison of depression, anxiety and life quality in acne
20
21 vulgaris patients who were treated with either isotretinoin or topical agents. *Int J*
22
23 *Dermatol* 2009;**48**:41-6.
24
- 25
26 34 Rehn LM, Meririnne E, Hook-Nikanne J, et al. Depressive symptoms and suicidal
27
28 ideation during isotretinoin treatment: a 12-week follow-up study of male Finnish
29
30 military conscripts. *J Eur Acad Dermatol Venereol* 2009;**23**:1294-7.
31
- 32
33 35 Simic D, Situm M, Letica E, et al. Psychological impact of isotretinoin treatment in
34
35 patients with moderate and severe acne. *Coll Antropol* 2009;**33 Suppl 2**:15-9.
36
- 37
38 36 McGrath EJ, Lovell CR, Gillison F, et al. A prospective trial of the effects of isotretinoin
39
40 on quality of life and depressive symptoms. *Br J Dermatol* 2010;**163**:1323-9.
41
- 42
43 37 Fakour Y, Noormohammadpour P, Ameri H, et al. The effect of isotretinoin (roaccutane)
44
45 therapy on depression and quality of life of patients with severe acne. *Iran J Psychiatry*
46
47 2014;**9**:237-40.
48
- 49
50 38 Ergun T, Seckin D, Ozaydin N, et al. Isotretinoin has no negative effect on attention,
51
52 executive function and mood. *J Eur Acad Dermatol Venereol* 2012;**26**:431-9.
53
54
55
56
57

- 1
2
3
4 39 Ormerod AD, Thind CK, Rice SA, et al. Influence of isotretinoin on hippocampal-based
5
6 learning in human subjects. *Psychopharmacology (Berl)* 2012;**221**:667-74.
7
8
9 40 Yesilova Y, Bez Y, Ari M, et al. Effects of isotretinoin on obsessive compulsive
10
11 symptoms, depression, and anxiety in patients with acne vulgaris. *J Dermatolog Treat*
12
13 2012;**23**:268-71.
14
15
16 41 Marron SE, Tomas-Aragones L, Boira S. Anxiety, depression, quality of life and patient
17
18 satisfaction in acne patients treated with oral isotretinoin. *Acta Derm Venereol*
19
20 2013;**93**:701-6.
21
22
23 42 Gnanaraj P, Karthikeyan S, Narasimhan M, et al. Decrease in "Hamilton Rating Scale for
24
25 Depression" Following Isotretinoin Therapy in Acne: An Open-Label Prospective
26
27 Study. *Indian J Dermatol* 2015;**60**:461-4.
28
29
30
31 43 Suarez B, Serrano A, Cova Y, et al. Isotretinoin was not associated with depression or
32
33 anxiety: A twelve-week study. *World J Psychiatry* 2016;**6**:136-42.
34
35
36
37 44 Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with
38
39 isotretinoin: a systematic review. *Semin Cutan Med Surg* 2007;**26**:210-20.
40
41
42 45 Vallerand IA, Lewinson RT. Efficacy and adverse events of oral isotretinoin for acne: a
43
44 systematic review. 2017;
45
46
47 46 Huang YC, Cheng YC. Isotretinoin treatment for acne and risk of depression: A
48
49 systematic review and meta-analysis. *J Am Acad Dermatol* 2017;**76**:1068-76.e9.
50
51
52 47 Crandall J, Sakai Y, Zhang J, et al. 13-cis-retinoic acid suppresses hippocampal cell
53
54 division and hippocampal-dependent learning in mice. *Proc Natl Acad Sci U S A*
55
56

- 1
2
3
4 2004;**101**:5111-6.
5
6 48 Bremner JD, Fani N, Ashraf A, et al. Functional brain imaging alterations in acne
7
8 patients treated with isotretinoin. *Am J Psychiatry* 2005;**162**:983-91.
9
10
11 49 O'Reilly KC, Trent S, Bailey SJ, et al. 13-cis-Retinoic acid alters intracellular serotonin,
12
13 increases 5-HT1A receptor, and serotonin reuptake transporter levels in vitro. *Exp Biol*
14
15 *Med (Maywood)* 2007;**232**:1195-203.
16
17
18 50 Misery L. Consequences of psychological distress in adolescents with acne. *J Invest*
19
20 *Dermatol* 2011;**131**:290-2.
21
22
23 51 Aktan S, Ozmen E, Sanli B. Anxiety, depression, and nature of acne vulgaris in
24
25 adolescents. *Int J Dermatol* 2000;**39**:354-7.
26
27
28 52 Yang YC, Tu HP, Hong CH. Female gender and acne disease are jointly and
29
30 independently associated with the risk of major depression and suicide: a national
31
32 population-based study. *BioMed Research International* 2014;**2014**:504279.
33
34
35 53 Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and
36
37 psychological morbidity in mid-adolescence: a community-based study. *Br J Dermatol*
38
39 2001;**145**:274-9.
40
41
42
43 54 Thiboutot D, Dreno B, Layton A. Acne counseling to improve adherence. *Cutis*
44
45 2008;**81**:81-6.
46
47
48 55 Hansen TJ, Lucking S, Miller JJ, et al. Standardized laboratory monitoring with use of
49
50 isotretinoin in acne. *J Am Acad Dermatol* 2016;**75**:323-8.
51
52
53
54
55
56
57
58
59
60

Table 1. Characteristics of included studies

Author (year)	Region	Design	Isotretinoin users	Mean/Median age (year)	Female (%)	Acne severity	Comparison groups	Dose	Treatment duration	Depression assessment
Kellett et al. (1999)	UK	Prospective	34	24	44	NA	Before vs after	1.0 mg/(kg · d)	4 months	HADS-D
Lick et al. (2000) a	Canada	Retrospective	7195	<30 (75%)	47	NA	Before vs after	40 mg (86%)	3–6 months (62%)	ICD code
Lick et al. (2000) b	UK	Retrospective	340	<30 (78%)	42	NA	Before vs after	20 mg (75%)	1–2 months (81%)	ICD code
Ng et al. (2002)	Australia	Prospective	174	20	41	Moderate to severe	Before vs after	0.8–1.0 mg/(kg · d)	6 months	BDI
Perahbas et al. (2004)	Turkey	Prospective	23	20	43	Severe	Before vs after	0.5–1.0 mg/(kg · d)	4 months	MADRS
Kellett et al. (2005)	UK	Prospective	33	25	36	NA	Before vs after	1.0 mg/(kg · d)	4 months	BDI
Kaymak et al. (2006)	Turkey	Prospective	24	100	58	Moderate	Before vs after	0.75–1.0 mg/(kg · d)	5–7 months	HRS
Chia et al. (2005)	USA	Prospective	59	12–19	25	Moderate to severe	Before vs after	1.0 mg/(kg · d)	3–4 months	CES-D

1														
2														
3														
4														
5														
6														
7	Azoulay	et al.	Canada	Retrospective	126	28	53	NA	Users vs nonusers	NA	5 months	ICD code		
8	(2008)			ve										
9														
10	Kaymak	et al.	Turkey	Prospective	37	21	69	Mild to severe	Before vs after	0.5–0.8 mg/(kg · d)	> 5 months	BDI, HADS-D		
11	(2009)													
12														
13														
14	Bozdog	et al.	Turkey	Prospective	50	20	52	Moderate to severe	Before vs after	1.0 mg/(kg · d)	4 months	BDI		
15	(2009)													
16														
17	Behn et al. (2009)		Finland	Prospective	126	20	0	Moderate to severe	Before vs after	0.5 mg/(kg · d)	3 months	BDI		
18														
19														
20														
21	Simic et al. (2009)		Bosnia and Herzegovina	Prospective	85	19	34	Moderate to severe	Isotretinoin vs vitamin C	1.0 mg/(kg · d)	2 months	BDI		
22														
23														
24														
25														
26	McGrath et al. (2010)		UK	Prospective	65	20	31	Mean AGS score 3.3	Before vs after	0.5–1.0 mg/(kg · d)	3 months	CES-D		
27														
28														
29														
30														
31	Ergun et al. (2012)		Turkey	Prospective	65	22	73	Severe or resistant	Before vs after	0.5–1.0 mg/(kg · d)	≈ 5 months	HADS-D		
32														
33														
34														
35	Ormerod et al. (2012)		UK	Prospective	16	22	25	Severe	Before vs after	0.5–1.0 mg/(kg · d)	3–6 months	BDI		
36														
37														
38														
39														
40														
41														
42														
43														
44														
45														
46														
47														

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

Yesilova et al. (2012)	Turkey	Prospective	43	23	70	Mild to severe	Before vs after	0.5–1.0 mg/(kg · d)	6 months	HADS-D
Marron et al. (2013)	Spain	Prospective	346	21	59	Moderate	Before vs after	Total: 120 mg/kg	7 months	HADS-D
Fakour et al. (2014)	Iran	Prospective	98	22	61	Severe	Before vs after	0.5 mg/(kg · d)	4 months	BDI
Gnanaraj et al. (2015)	India	Prospective	143	21	34	Moderate to severe	Before vs after	0.5 mg/(kg · d)	3 months	HRS
Suarez et al. (2016)	Venezuela	Prospective	36	21	44	Severe (25%)	Before vs after	30 mg/d	3 months	ZDS

24 AGS, Acne grading scale; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS-D, hospital
25 anxiety and depression scale-depression; HRS, Hamilton Rating Scale; ICD, International Classification of Diseases; MADRS, Montgomery–
26 Asberg depression rating scale; NA, not available; ZDS, Zung self-rating depression scale.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Table 2. Subgroup analysis for studies presenting depressive symptom scores after isotretinoin compared with the baseline

Subgroups	Number of cohorts	SMD (95% CI)	<i>P</i> value	<i>I</i> ² (<i>P</i> value)
Region				
Europe	14	-0.35 (-0.51 to -0.19)	<0.05	46.3% (<0.05)
Asia	3	-0.18 (-0.81 to 0.45)	0.57	94.4% (<0.05)
North America	1	-0.23 (-0.59 to 0.13)	0.21	–
Africa	1	-0.74 (-1.22 to -0.26)	<0.05	–
Depression scale				
BDI	10	0.10 (-0.12 to 0.32)	0.38	65.2% (<0.05)
HADS-D	4	-0.57 (0.31–0.83)	<0.05	27.2% (0.25)
CES-D	2	0.27 (0.02–0.52)	<0.05	0% (0.78)
HRS	2	0.55 (-0.46 to 1.56)	0.29	96.6% (<0.05)
MADRS	1	0.33 (-0.25 to 0.91)	0.27	–
ZDS	1	0.74 (0.26–1.22)	<0.05	–
Sample size				
<50	9	-0.38 (-0.65 to -0.12)	<0.05	64.0% (<0.05)
≥50	11	-0.29 (-0.54 to -0.04)	<0.05	83.1% (<0.05)
Percentage of female patients				
<50	12	-0.32 (-0.55 to -0.09)	<0.05	76.8% (<0.05)

1
2
3 ≥ 50 8 $-0.34 (-0.04 \text{ to } -0.64)$ <0.05 78.4% (<0.05)
4
5

6 BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression
7 Scale; CI, confidence interval; HADS-D, hospital anxiety and depression scale-depression;
8 HRS, Hamilton Rating Scale; MADRS, Montgomery–Asberg depression rating scale; SMD,
9 standardized mean difference; ZDS, Zung self-rating depression scale.
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4 **Figure legends:**
5

6 **Figure 1.** Study selection process.
7

8 **Figure 2.** Forest plot showing the standardized mean difference for the comparison of
9 depression symptom scores before and after isotretinoin treatment in patients with acne.
10
11

12 **Figure 3.** Funnel plot of studies comparing depression symptom scores before and after
13 isotretinoin treatment in patients with acne.
14
15

16 **Figure 4.** Forest plot showing the weighted mean difference for the comparison of BDI
17 scores before and after isotretinoin treatment in patients with acne.
18
19

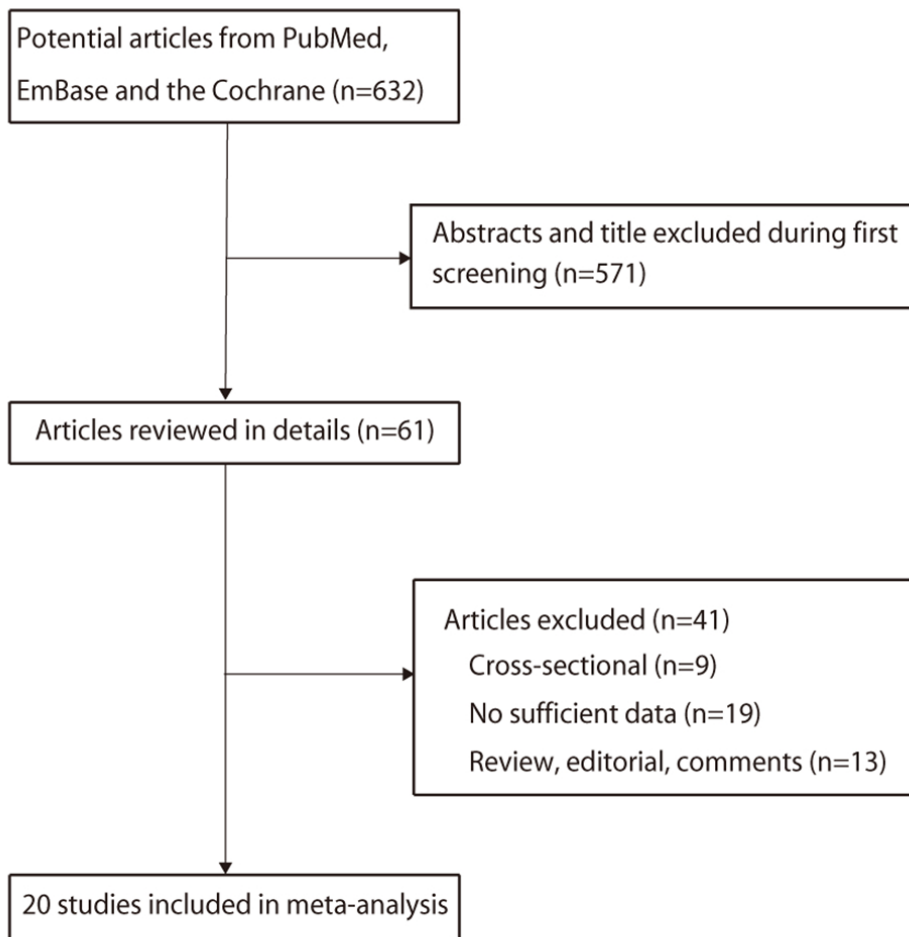
20 **Figure 5.** Forest plot showing the association between isotretinoin treatment and depression
21 in patients with acne.
22
23

24 **Figure 6.** Funnel plot showing the association between isotretinoin treatment and
25 depression in patients with acne.
26
27

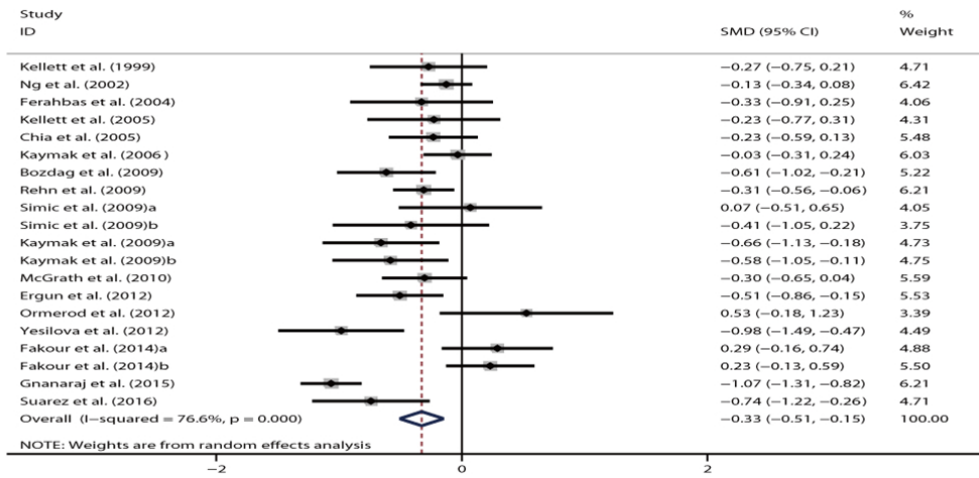
28
29
30
31
32
33
34
35
36 **Legends for supporting information**

37
38
39 **Supplemental 1.** The details of searching strategy in PubMed.
40

41
42 **Supplemental 2.** Newcastle–Ottawa Scale for quality assessment of included studies
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

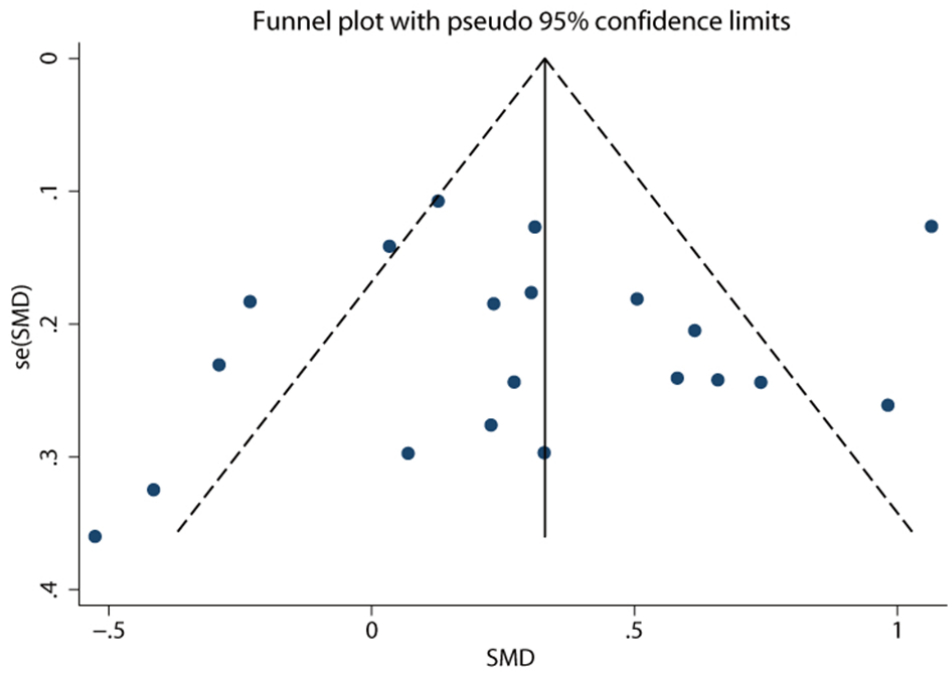


83x85mm (300 x 300 DPI)

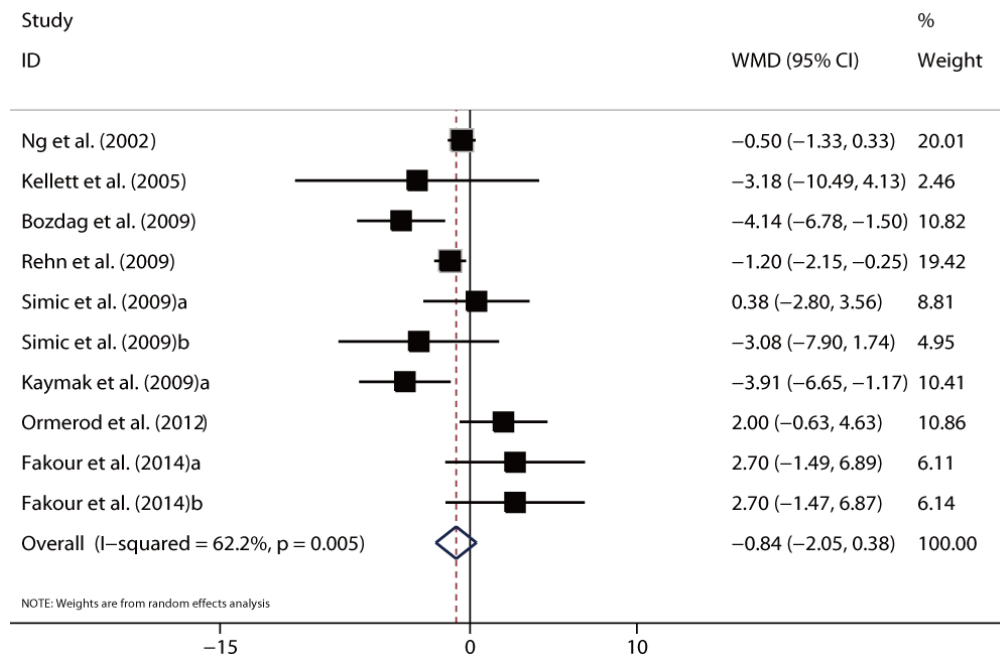


83x39mm (300 x 300 DPI)

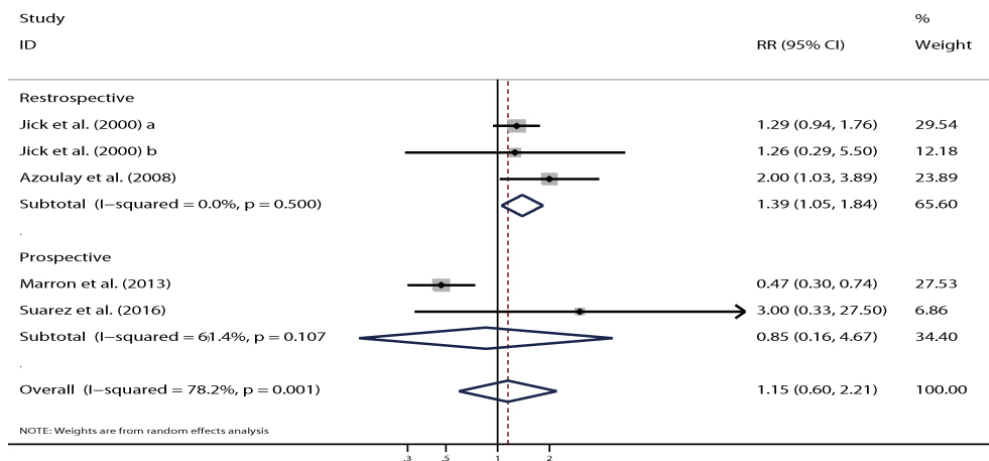
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



83x58mm (300 x 300 DPI)

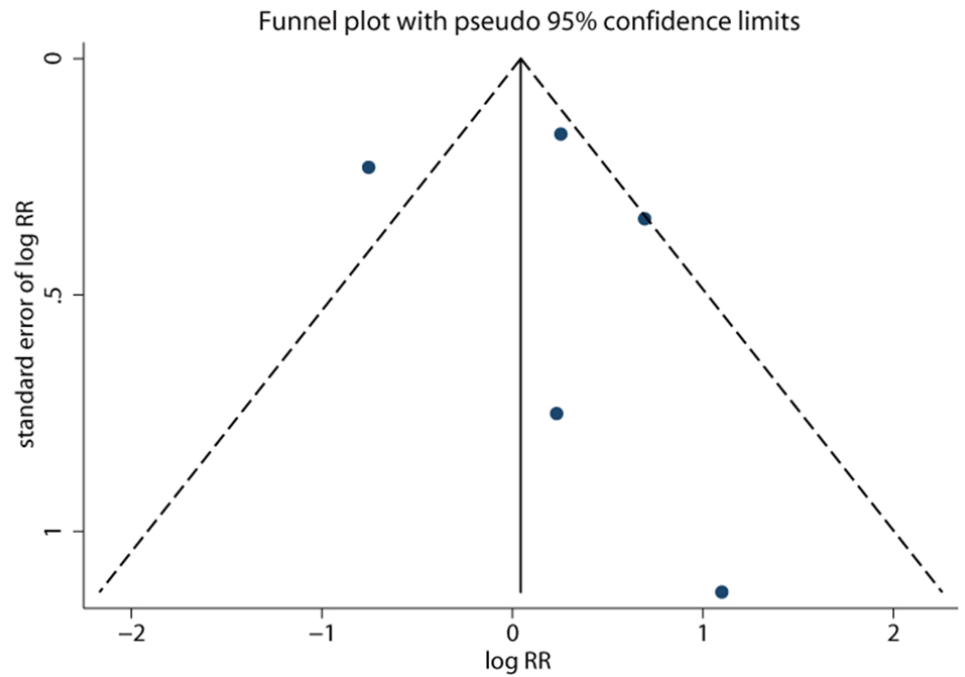


83x56mm (300 x 300 DPI)



83x38mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



83x57mm (300 x 300 DPI)

Searching strategy in PubMed:

((("depression"[Mesh] OR "depression") OR "depressive"[Mesh] OR "depressive") AND
("acne"[Mesh] OR "acne") AND ("isotretinoin"[Mesh] OR "isotretinoin"))

For peer review only

1
2
3
4 **Use of isotretinoin and risk of depression in patients with acne: a systematic**
5
6 **review and meta-analysis**
7

8
9 Changqiang Li², Jianmei Chen¹, Wo Wang³, Ming Ai¹, Qi Zhang¹, Li Kuang^{1*}
10

11
12 ¹Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical
13
14 University, Chongqing 400016, China
15

16
17 ²Department of Dermatology, The Affiliated Hospital of Southwest Medical
18
19 University, Luzhou , 646000, China
20

21
22 ³Mental Health Center, University-Town Hospital of Chongqing Medical University,
23
24 Chongqing 401331, China
25

26
27
28
29
30 *Corresponding author:

31
32 Li Kuang
33

34
35 Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical
36
37 University, Chongqing 400016, China
38

39
40 Tel: +86-13908379733
41

42
43 Fax: +86-21-64085875
44

45
46 Email: kuangli0308120@126.com
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Supplemental Table 1. Newcastle–Ottawa scale for quality assessment of included studies

Study	Selection	Comparability	Outcome
Kellett et al. (1999)	****	*	***
Jick et al. (2000) a	****	**	**
Jick et al. (2000) b	****	**	**
Ng et al. (2002)	****	*	***
Ferahbas et al. (2004)	****	*	***
Kellett et al. (2005)	****	*	***
Kaymak et al. (2006)	****	*	***
Chia et al. (2005)	***	*	***
Azoulay et al. (2008)	****	**	**
Kaymak et al. (2009)	****	*	***
Bozdog et al. (2009)	****	*	***
Rehn et al. (2009)	***	*	***
Simic et al. (2009)	****	*	***
McGrath et al. (2010)	****	*	***
Ergun et al. (2012)	****	*	***
Ormerod et al. (2012)	***	*	***
Yesilova et al. (2012)	****	*	***
Marron et al. (2013)	****	*	***
Fakour et al. (2014)	****	*	***
Gnanaraj et al. (2015)	****	*	***
Suarez et al. (2016)	****	*	***



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS and length of follow-up) and report characteristics (e.g., years considered, language, and publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage and contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS and funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio and difference in means).	4–5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4–5



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias and selective reporting within studies).	4–5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses and meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, and follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	6–7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6–7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6–7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses and meta-regression [see Item 16]).	6–7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	7–9
Limitations	25	Discuss limitations at study and outcome levels (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research and reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

BMJ Open

Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021549.R2
Article Type:	Research
Date Submitted by the Author:	22-Nov-2018
Complete List of Authors:	Li, Changqiang ; the Affiliated Hospital of Southwest Medical University, Department of Dermatology Chen, Jianmei ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Wang, Wo ; University-Town Hospital of Chongqing Medical University, Mental Health Center Ai, Ming ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Zhang, Qi ; the First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Kuang, Li
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Dermatology
Keywords:	Acne < DERMATOLOGY, Depression & mood disorders < PSYCHIATRY, ORAL MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4 **Use of isotretinoin and risk of depression in patients with acne: a systematic review and**
5
6 **meta-analysis**
7

8
9 Changqiang Li², Jianmei Chen¹, Wo Wang³, Ming Ai¹, Qi Zhang¹, Li Kuang^{1*}
10

11
12 ¹Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical University,
13
14 Chongqing 400016, China
15

16
17 ²Department of Dermatology, the Affiliated Hospital of Southwest Medical University,
18
19 Luzhou646000, China
20

21
22 ³Mental Health Center, University-Town Hospital of Chongqing Medical University,
23
24 Chongqing 401331, China
25

26
27
28
29
30 ***Corresponding author:**
31

32
33 Li Kuang
34

35
36 Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical University,
37
38 Chongqing 400016, China
39

40
41 Tel: +86-13908379733
42

43
44 Fax: +86-21-64085875
45

46
47 Email: kuangli0308@163.com
48
49

50
51 **Running title:** Isotretinoin and risk of depression in patients with acne
52
53
54
55
56
57
58
59
60

ABSTRACT

Objective: This study aimed to investigate the association between the use of isotretinoin and the risk of depression in patients with acne.

Design: This was a meta-analysis in which the standardized mean difference (SMD) and the relative risk (RR) were used for data synthesis employed the random-effects model.

Setting: Studies were identified via electronic searches of PubMed, Embase, and the Cochrane Library from inception up to December 28, 2017.

Participants: Patients with acne.

Interventions: Studies comparing isotretinoin with other interventions in patients with acne were included.

Results: Twenty studies were selected. The analysis of 17 studies showed a significant association of the use of isotretinoin with improved symptoms compared with the baseline before treatment [SMD = -0.33, 95% confidence interval (CI) -0.51 to -0.15, $P < 0.05$; $I^2 = 76.6\%$, $P < 0.05$]. Four studies were related to the analysis of the risk of depression. The pooled data indicated no association of the use of isotretinoin with the risk of depressive disorders (RR = 1.15, 95% CI 0.60–2.21, $P = 0.14$). The association of the use of isotretinoin with the risk of depressive disorders was statistically significant on pooling retrospective studies (RR = 1.39, 95% CI 1.05–1.84, $P = 0.02$), but this association was not evident on pooling prospective studies (RR = 0.85, 95% CI 0.60–2.21, $P = 0.86$).

1
2
3
4 **Conclusions:** This study suggested an association of the use of isotretinoin in patients with
5
6 acne with significantly improved depression symptoms. Future randomized controlled trials
7
8 are needed to verify the present findings.
9
10

11 12 13 14 15 **Strengths and limitations of this study**

- 16
17
18 1. Most included studies were prospectively designed, and the quality of included studies was
19
20 largely moderate to high.
21
22
23 2. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses.
24
25
26 3. The small sample sizes of some included studies might have limited the statistical power and
27
28 increased the chance of missing small effects.
29
30
31 4. No randomized controlled trial was available so far, which was a major drawback for studies
32
33 on this topic.
34
35
36 5. The treatment duration, drug dose, and depression scale varied between different studies.
37
38
39
40
41

42 **Key words:** acne; depression; isotretinoin; meta-analysis
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit of the face, neck, chest, and back ¹. As a pleomorphic skin disease, it may present as noninflammatory lesions (open and closed comedones) or inflammatory lesions (papules, pustules, or nodules) ². It is the most common skin disease around the world, with an estimated prevalence of 70%–87% ³.

The economic burden of acne is substantial. The cost is estimated to exceed \$1 billion per year in the United States for direct acne therapy, with \$100 million spent on various acne products ⁴. Acne vulgaris may cause cosmetic defects and significantly impact the quality of life ⁵. It may provoke a wide range of mental problems, including depression, anxiety, poor self-esteem, social phobia, and even suicidal attempts ⁶.

The optimal treatment approach depends on the morphology and severity of acne. Mild cases are suggested to be treated with topical retinoids. For moderate cases, systemic drugs are always needed, including oral antibiotics, hormonal therapy, and oral retinoids. However, for severe or resistant moderate acne, isotretinoin is the treatment of choice ^{1,2,4,7}. Isotretinoin is a vitamin A-derivative 13-*cis*-retinoic acid, which is the most effective therapy for acne to date. It targets all four processes during acne development, including normalization of follicular desquamation, reduction of sebaceous gland activity, inhibition of the proliferation of *Propionibacterium acnes*, and anti-inflammatory effects ^{2,7,8}. The meta-analysis suggested that isotretinoin cured around 85% of patients after an average treatment course of 4 months ⁹.

Depressive disorders are highly prevalent in the Western world. The lifetime prevalence of major depressive disorders in the United States and Western Europe is around 13%–16% ¹⁰.

1
2
3
4 The frequency of depressive disorders during the use of isotretinoin varies from 1% to 11% ¹¹.
5
6
7 Theoretically, effective treatment may lead to an improvement in depressive symptoms of
8
9 patients with acne. However, the use of systemic isotretinoin itself may potentially increase the
10
11 risk of depression ¹². Experimental studies showed that isotretinoin could affect the central
12
13 nervous system and was involved in the pathogenesis of depression ¹³. However, some
14
15 researchers disputed that the risk was extremely small and might be influenced by the
16
17 background risk or nondrug confounding factors ¹². The evidence for this controversy remained
18
19 incomplete and unclear. Therefore, this systematic review and meta-analysis was performed to
20
21 explore the association between the use of isotretinoin and the risk of depression among
22
23 patients with acne. Further, whether this relationship differed in patients with specific
24
25 characteristics was also explored.
26
27
28
29
30
31
32
33
34
35
36

37 **METHODS**

38 **Literature search**

39
40
41
42 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was
43
44 followed to conduct this meta-analysis ¹⁴. A literature search for articles published between
45
46 May 1984 and December 28, 2017, was performed using PubMed, Embase, and the Cochrane
47
48 Library. The following groups of keywords were used in the search: (“depression” OR
49
50 “depressive”) AND “acne” AND “isotretinoin.” The details of searching strategy in PubMed
51
52 are presented in Supplemental 1. Also, a manual search of references listed in included studies
53
54
55
56
57
58
59
60

1
2
3
4 and published reviews were also performed to search for potentially eligible studies. The
5
6 language was restricted to English.
7

8 9 **Selection criteria**

10
11 Studies were included if they fulfilled the following criteria: (1) being randomized controlled
12
13 trial (RCT), prospective or retrospective study, nested case–control study, or population-based
14
15 case–control study; (2) comparing the outcomes before and after the use of isotretinoin in
16
17 patients with acne; or comparing isotretinoin with other treatment regimens in patients with
18
19 acne; (3) presenting the change in depressive symptoms measured using a continuous
20
21 depression scale ¹⁵; or reporting the number of depressive patients before and after the use of
22
23 isotretinoin; or directly presenting the relative risk (RR), odds ratio (OR), or hazard ratio (HR)
24
25 between the use of isotretinoin and the risk of depression.
26
27
28
29
30
31
32

33 **Data extraction and quality assessment**

34
35 Two authors independently assessed the titles and abstracts for eligibility and extracted data in
36
37 standardized electronic tables. The following data were extracted from included studies:
38
39 publication year, author, study design, sample size, participant sex and age, severity of acne,
40
41 compared groups, dose and duration of isotretinoin, and depression assessment tool. The
42
43 quality of included studies was assessed using the 9-star Newcastle–Ottawa Scale. This scale
44
45 evaluated the study quality based on three parameters: selection, comparability, and exposure
46
47 (case–control study) or outcome (cohort study). A maximum of 4 points was assigned for the
48
49 item of selection, 2 points for comparability, and 3 points for exposure/outcome ¹⁶. Studies
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 were deemed as high quality for a score of 8–9, moderate quality for a score of 6–7, and low
5
6 quality for a score ≤ 5 .
7
8

9 **Statistical analysis**

10
11
12 The continuous outcome of interest was the alteration in depressive symptoms assessed using
13
14 a continuous depression scale after the use of isotretinoin. For the continuous parameter of
15
16 depression score, the means and standard differences (SD) of the scores were extracted. The
17
18 standard mean difference (SMD) was used as the outcome measure. The SMD was a unitless
19
20 effect size estimate, which was the mean difference in the depression score between the
21
22 compared groups divided by the pooled SD of the distribution of the score used in the study.
23
24
25 The conversion of median (range/interquartile range) to mean \pm SD was done by a previously
26
27 proposed method ¹⁷. The binary outcome of interest was the number of participants whose
28
29 conditions were regarded as depression. RR and its corresponding 95% confidence interval
30
31 (CI) were used as the outcome measure. HR was regarded as equivalent to RR in cohort studies.
32
33
34 Given the overall low incidence of depression among the general population, OR was assumed
35
36 to be an accurate estimate of RR. It was preferred to use the effect measures that reflected the
37
38 greatest degree control for confounding factors. Both adjusted and crude data were analyzed.
39
40
41 When data on different subgroups were reported by the same cohort, they were first pooled
42
43 using the fixed-effects model. As the random-effects model was more robust than the fixed-
44
45 effects model, the DerSimonian–Laird random-effects model was used to calculate the overall
46
47 effect estimates for the association between the use of isotretinoin and the risk of depression
48
49
50
51
52
53
54
55
56
57
58
59
60
18. The heterogeneity was evaluated using the Cochrane Q test and the I^2 statistic. Heterogeneity

1
2
3
4 was considered low, moderate, or high for $I^2 < 25\%$, $25\%–50\%$, and $>50\%$, respectively ^{19, 20}.

5
6 Subgroup analyses were conducted based on the following confounders: region, study design,
7
8 sample size, female percentage, and depression scale. Furthermore, meta-regression analyses
9
10 were performed for the continuous confounders of sample size and female percentage. A
11
12 sensitivity analysis was conducted by excluding a single study at a time. Also, a sensitivity
13
14 analysis was conducted using the weighted mean difference (WMD) as the effect estimate for
15
16 studies employing the same depression symptom scale. The publication bias was visually
17
18 assessed by constructing a funnel plot and statistically assessed using the Begg's and Egger's
19
20 regression asymmetry tests ^{21, 22}. All statistical analyses were conducted using the software
21
22 Stata 12.0 (StataCorp, TX, USA). A *P* value less than 0.05 was considered statistically
23
24 significant.
25
26
27
28
29
30
31
32

33 **Patient and public involvement statement**

34
35 Patients and the public were not involved
36
37
38
39
40
41
42

43 **RESULTS**

44 **Study selection**

45
46 A total of 632 records were retrieved from the electronic search, including 145 studies from
47
48 PubMed, 469 records from Embase, and 18 records from the Cochrane Library. After screening
49
50 by titles and abstracts, 571 studies were excluded for the following reasons: reviews, editorials,
51
52 case reports, or irrelevant studies, leaving 61 studies for full-text review. Nine cross-sectional
53
54 studies, 19 studies without sufficient data, and 13 review, editorial, or comments were excluded.
55
56
57
58
59
60

1
2
3
4 Finally, 20 studies were pooled into the meta-analysis ²³⁻⁴³. A flow diagram of the study
5
6 selection process is depicted in Figure 1.
7
8

9 10 **Study characteristics**

11
12 The characteristics of the included 20 studies are shown in Table 1. Jick et al. reported two
13
14 independent cohorts ²⁴, which were analyzed separately. Except for two retrospective studies
15
16 identifying depressive patients using the International Classification of Diseases code ^{24, 31},
17
18 other studies were prospectively designed, and depression was assessed using depression
19
20 symptom scales. The number of participants using isotretinoin ranged from 16 to 7195. The
21
22 enrolled patients with acne were distributed around the world, including 14 cohorts from
23
24 Europe, 3 from North America, 3 from Asia, and 1 from Africa. The percentage of female
25
26 patients ranged from 0% to 73%. Most studies compared data before and after the use of
27
28 isotretinoin, except for two studies. Simic et al. compared isotretinoin with vitamin C ³⁵.
29
30 Azoulay et al. compared isotretinoin users with nonusers ³¹. Most studies prescribed
31
32 isotretinoin for moderate-to-severe acne. The dose of isotretinoin ranged largely from 0.5 to
33
34 1.0 mg/(kg · d). The duration of the use of isotretinoin ranged from around 1 month to about
35
36 half a year. The quality of included studies is shown in Supplemental 2. Most studies had
37
38 satisfactorily high quality. The least satisfactory item was the adjustment of the confounding
39
40 factors.
41
42
43
44
45
46
47
48
49
50
51

52 53 **Change in depression symptom scores after treatment**

54
55 Seventeen studies reported the depression symptom scores before and after the use of
56
57 isotretinoin. All studies were prospectively designed. Simic et al. (2009) presented data for
58
59
60

1
2
3
4 moderate and severe acne³⁵. Fakour et al. showed data for males and females separately³⁷.
5
6
7 Kaymak et al. reported depression scores measured using Beck Depression Inventory (BDI)
8
9 and hospital anxiety and depression scale-depression (HADS-D) scales³³. These subgroup data
10
11 were all pooled into the overall analysis. Compared with the baseline condition before therapy,
12
13 the use of isotretinoin was associated with a significant improvement in depressive symptoms
14
15 (SMD = -0.33, 95% CI -0.51 to -0.15, $P < 0.05$) (Fig. 2). Highly significant heterogeneity
16
17 was revealed ($I^2 = 76.6%$, $P < 0.05$).
18
19
20
21
22

23 In the sensitivity analysis, the overall effect was not substantially altered when excluding any
24
25 single study. In the meta-regression analysis, the number of included participants ($P = 0.995$)
26
27 and the female proportion ($P = 0.56$) did not account for the source of heterogeneity. Data on
28
29 subgroup analyses are shown in Table 2. The pooled effect estimate remained significant for
30
31 14 European studies (SMD = -0.35, 95% CI -0.51 to -0.19, $P < 0.05$), with moderate
32
33 heterogeneity ($I^2 = 46.3%$). However, the analysis of three Asian studies did not show
34
35 significant results (SMD = -0.18, 95% CI -0.81 to 0.45, $P = 0.57$; $I^2 = 94.4%$). The use of
36
37 isotretinoin had no significant effect on depressive symptoms in North America (SMD = -0.23,
38
39 95% CI -0.59 to 0.13; $P = 0.21$), while it was associated with improved depressive symptoms
40
41 in Africa (SMD = -0.74, 95% CI -1.22 to -0.26, $P < 0.05$). The pooled results remained
42
43 significant for studies using HADS-D (SMD = -0.57, 95% CI -0.83 to -0.31, $P < 0.25$; $I^2 =$
44
45 27.2%), and those using the Center for Epidemiological Studies Depression scale (CES-D)
46
47 (SMD = -0.27, 95% CI -0.52 to -0.02, $P < 0.05$; $I^2 = 0%$). However, the pooled effect turned
48
49 to be nonsignificant for studies using the BDI scale (SMD = -0.15, 95% CI -0.36 to 0.06, $P =$
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 0.17; $I^2 = 62.4\%$) and those using the Hamilton Rating Scale (HRS) (SMD = -0.55 , 95% CI
5
6 -1.56 to 0.46 , $P = 0.29$; $I^2 = 96.6\%$). The pooled effects were significant for both studies with
7
8 a smaller sample size (SMD = -0.38 , 95% CI -0.65 to -0.12 , $P < 0.05$) and those with a larger
9
10 sample size (SMD = -0.29 , 95% CI -0.54 to -0.04 , $P < 0.05$). The results for different
11
12 proportions of females did not show a significant difference. The funnel plot appeared to be
13
14 symmetrical (Fig. 3). No publication bias was revealed using the Egger's test ($P = 0.76$) or the
15
16 Begg's test ($P = 0.87$).

17
18 Also, the sensitivity analysis was performed by pooling the WMD for studies using the same
19
20 scale. The pooled results were nonsignificant for studies using the BDI scale (WMD = -0.84 ,
21
22 95% CI -2.05 to 0.38 , $P = 0.18$; $I^2 = 62.2\%$, $P < 0.05$) (Fig. 4) and those using HRS (WMD =
23
24 -1.91 , 95% CI -5.44 to 1.63 , $P = 0.29$; $I^2 = 97.3\%$, $P < 0.05$). In contrast, the pooled WMDs
25
26 were significant for studies using HADS-D (WMD = -2.06 , 95% CI -3.42 to -0.70 , $P < 0.05$;
27
28 $I^2 = 66.0\%$, $P < 0.05$) and those using CES-D (WMD = -1.88 , 95% CI -3.64 to -0.11 , $P <$
29
30 0.05 ; $I^2 = 0\%$, $P = 0.63$).

41 42 **Use of isotretinoin and risk of depression**

43
44 Two retrospective studies showed the adjusted RR for the association between the use of
45
46 isotretinoin and the risk of depression^{24, 31}. Jick et al. presented data for two independent
47
48 cohorts. The overall result of three cohorts showed that the use of isotretinoin was associated
49
50 with an increased risk of depression (RR = 1.39 , 95% CI 1.05 – 1.84 , $P = 0.02$; Fig. 5), and no
51
52 significant heterogeneity was shown ($I^2 = 0.0\%$, $P = 0.50$). However, no significant difference
53
54 was noted in the relationship between isotretinoin use and the risk of depression on pooling
55
56
57
58
59
60

1
2
3
4 two prospective studies (RR = 0.85, 95% CI 0.60–2.21, $P = 0.86$; Fig. 5), and a substantial
5
6 heterogeneity was observed ($I^2 = 61.4\%$, $P = 0.11$). The funnel plot appeared to be symmetrical
7
8 (Fig. 6), and the Egger's test ($P = 0.76$) or the Begg's test ($P = 1.00$) suggested no evidence of
9
10 potential publication bias.
11
12
13
14
15
16

17 **DISCUSSION**

18
19
20 The risk of depression associated with the use of isotretinoin in patients with acne has been a
21
22 major concern for a long time. Previous data showed conflicting and inconsistent results. This
23
24 meta-analysis assessed the association between the use of isotretinoin and the risk of depression.
25
26 It had several strengths as follows. A comprehensive database search of worldwide cohorts was
27
28 conducted, enrolling a large number of participants. The quality of included studies was largely
29
30 moderate to high. Most included studies were prospectively designed. The association was
31
32 investigated from several aspects. The heterogeneity was explored by sensitivity, subgroup,
33
34 and meta-regression analyses. The present findings showed that isotretinoin improved in
35
36 depressive symptoms in patients with acne. The benefit remained marked for studies using
37
38 HADS-D and CES-D. In risk assessment, the summary RR showed that the use of isotretinoin
39
40 was associated with an increased risk of depression in patients with acne on pooling
41
42 retrospective studies, while this significant difference was not observed on pooling prospective
43
44 studies.
45
46
47
48
49
50
51
52
53

54
55 Two previous systematic reviews on this topic were identified^{13, 44}. They showed conflicting
56
57 results, and hence the association between isotretinoin use and depression remained
58
59
60

1
2
3
4 controversial. Further, although comprehensive scenarios were presented, data synthesis to
5
6 obtain pooled results could not be conducted. Vallerand conducted a systematic review based
7
8 on 11 trials to evaluate the efficacy and safety of oral isotretinoin for acne. Oral isotretinoin
9
10 significantly reduced the counts of acne lesions but increased the frequency of psychiatric
11
12 adverse events (depressed mood, fatigue, hallucination, insomnia, and lethargy; 32 vs 19).
13
14 However, this study did not provide the result by data synthesis ⁴⁵. Further, Huang et al
15
16 conducted a meta-analysis based on 31 studies and suggested that the use of isotretinoin did
17
18 not affect the incidence of depression. Further, they showed that the treatment of acne could
19
20 ameliorate depressive symptoms. However, the study summarized the investigated outcomes
21
22 using the depression assessment tool. Whether these relationships differed according to the
23
24 region, study design, sample size, and the female percentage was not illustrated ⁴⁶. Therefore,
25
26 the present study was conducted to evaluate any potential impact of the use of isotretinoin on
27
28 depression incidence and change in the depression score.
29
30
31
32
33
34
35
36
37
38

39 The concern for negative mood arose from a series of experimental studies. Oral isotretinoin
40
41 significantly suppressed cell division in the hippocampus and severely disrupted the learning
42
43 capacity of mice ⁴⁷. Bremner et al. found that the use of isotretinoin, but not antibiotics, was
44
45 associated with decreased brain metabolism in the orbitofrontal cortex, which was known to
46
47 mediate depression symptoms ⁴⁸. O'Reilly et al. proved that isotretinoin altered intracellular
48
49 serotonin level and increased 5-HT1A receptor and serotonin reuptake transporter levels *in*
50
51 *vitro* ⁴⁹. Thus, theoretically, isotretinoin itself might cause depressive disorders. However, the
52
53 potentially increased risk of depression could be compensated by the beneficial effects of
54
55
56
57
58
59
60

1
2
3
4 isotretinoin on patients with acne. Most patients with acne were worried about their
5
6
7 appearances, which might lead to a series of psychological disorders. It was inferred that the
8
9
10 improvement in depression symptoms after the use of isotretinoin might be attributed to the
11
12 treatment success. Also, isotretinoin had a gradual effect on mood over time, which was not an
13
14 acute event ⁵⁰.

15
16
17 Of note, the controversy over this topic was complicated by various confounding psychosocial
18
19 and clinical factors. Aktan et al. suggested that adolescent girls were more vulnerable to the
20
21 negative psychological effects of acne compared with boys ⁵¹. Women with acne were
22
23 significantly more embarrassed about their skin disease compared with males. A large database
24
25 study showed that female gender and acne could jointly increase the risk of depression ⁵².
26
27 However, the role of gender was not revealed in meta-regression and subgroup analyses. Acne
28
29 itself can exert different impacts on individual patients. The lack of knowledge, especially
30
31 about prognosis, may be a source of depression ^{24, 53}. Approximately one fifth of patients with
32
33 acne suffered from psychiatric disorders ³³. Better health education and care are important
34
35 components for treating patients with acne. They help eliminate the patients' misconceptions
36
37 about the disease and unrealistic treatment expectations ⁵⁴. The psychological interventions
38
39 may vary between different clinical settings and lead to a bias in the effect of isotretinoin.
40
41 Besides, data on the efficacy or side effect of the use of isotretinoin were insufficient in most
42
43 included studies. Isotretinoin may cause teratogenic toxicity. Contraceptives are recommended
44
45 for female users of fertile age to prevent pregnancy until the completion of the treatment ⁴¹.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 The levels of blood cholesterol and liver enzymes may be abnormal and should be monitored
5
6 during the treatment phase ⁵⁵.
7
8

9 This meta-analysis had several shortcomings. The sample sizes of some included studies were
10
11 still small, which might have limited the statistical power and increased the chance of missing
12
13 small effects. The current pooled analysis based on observational studies and no RCT was
14
15 available, which may overestimate the association between isotretinoin use and depression risk.
16
17 Moreover, included study designed as observational design might have a bias caused by
18
19 participant selection and confounding factors. Ideally, RCTs comparing isotretinoin with
20
21 placebo or other agents may provide more robust findings, whereas most included studies
22
23 compared the before- and after-treatment data. However, leaving patients with moderate-to-
24
25 severe acne without the use of isotretinoin may be unfair and even not ethical. Additionally,
26
27 the treatment duration, drug dose, and depression scale varied between different studies. The
28
29 acne severity or the dose of isotretinoin varied and was not reported by several studies. Patients
30
31 with severe acne or scars or those unresponsive to therapy might have a worse depressive mood.
32
33 However, the analyses for these confounding factors were insufficient in most studies.
34
35 Approximately one fifth of patients with acne suffered from psychiatric disorders ³³. Also,
36
37 some studies were sponsored by corporations ²⁴, which might have underestimated the
38
39 incidence of depressive disorders. Finally, although a greater risk of depression was associated
40
41 with the use of isotretinoin on pooling retrospective studies, selection and recall biases might
42
43 have affected the incidence of depression. Further, these conclusions might be unreliable
44
45 because smaller cohorts were included in such subsets.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 This meta-analysis showed that patients might have improved depressive symptoms after the
5
6 use of isotretinoin. Further, the use of isotretinoin in patients with acne did not contribute to
7
8 the development of depression. However, the summary results of retrospective studies
9
10 suggested that the use of isotretinoin in patients with acne might increase the risk of depression.
11
12
13
14
15 Future prospective controlled trials are warranted to verify the present findings.
16
17

20 **Funding**

21
22 Not applicable.
23
24
25
26
27

28 **Conflicts of interest statement**

29
30 Not declared.
31
32
33
34
35

36 **Author contributions**

37
38
39 CQL and LK contributed to conception and design. CQL, JMC, WW, MA, QZ, and LK
40
41 contributed to data acquisition or analysis and interpretation of data. CQL, JMC, WW, MA,
42
43 QZ, and LK were involved in drafting the manuscript or revising it critically for important
44
45 intellectual content. All authors have given final approval of the version to be published.
46
47
48
49
50
51

52 **Data sharing statement**

53
54
55 Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi:
56
57
58 10.5061/dryad.ft545hs
59
60

REFERENCES

- 1 Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet* 2012;**379**:361-72.
- 2 Katsambas AD, Stefanaki C, Cunliffe WJ. Guidelines for treating acne. *Clin Dermatol* 2004;**22**:439-44.
- 3 Dreno B, Poli F. Epidemiology of acne. *Dermatology* 2003;**206**:7-10.
- 4 James WD. Clinical practice. Acne. *N Engl J Med* 2005;**352**:1463-72.
- 5 Thomas DR. Psychosocial effects of acne. *J Cutan Med Surg* 2004;**8 Suppl 4**:3-5.
- 6 Saitta P, Keehan P, Yousif J, et al. An update on the presence of psychiatric comorbidities in acne patients, Part 2: Depression, anxiety, and suicide. *Cutis* 2011;**88**:92-7.
- 7 Dawson AL, Dellavalle RP. Acne vulgaris. *BMJ* 2013;**346**:f2634.
- 8 Chivot M. Retinoid therapy for acne. A comparative review. *Am J Clin Dermatol* 2005;**6**:13-9.
- 9 Wessels F, Anderson AN, Kropman K. The cost-effectiveness of isotretinoin in the treatment of acne. Part 1. A meta-analysis of effectiveness literature. *S Afr Med J* 1999;**89**:780-4.
- 10 Kurek A, Johanne Peters EM, Sabat R, et al. Depression is a frequent co-morbidity in patients with acne inversa. *J Dtsch Dermatol Ges* 2013;**11**:743-9, 43-50.
- 11 Borovaya A, Olisova O, Ruzicka T, et al. Does isotretinoin therapy of acne cure or cause depression? *Int J Dermatol* 2013;**52**:1040-52.
- 12 Wolverton SE, Harper JC. Important controversies associated with isotretinoin therapy for acne. *Am J Clin Dermatol* 2013;**14**:71-6.
- 13 Kontaxakis VP, Skourides D, Ferentinos P, et al. Isotretinoin and psychopathology: a review. *Ann Gen Psychiatry* 2009;**8**:2.

- 1
2
3
4 14 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and
5
6 meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.
7
8
9 15 Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck Depression
10
11 Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D),
12
13 Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and
14
15 Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)* 2011;**63 Suppl**
16
17 **11**:S454-66.
18
19
20
21
22 16 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing
23
24 the quality of nonrandomised studies in meta-analyses.
25
26 http://www.ohrica/programs/clinical_epidemiology/oxfordasp
27
28
29
30
31 17 Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the
32
33 sample size, median, range and/or interquartile range. *BMC Med Res Methodol*
34
35 2014;**14**:135.
36
37
38
39 18 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177-
40
41 88.
42
43
44
45 19 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*
46
47 2003;**327**:557-60.
48
49
50 20 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*
51
52 2002;**21**:1539-58.
53
54
55 21 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication
56
57 bias. *Biometrics* 1994;**50**:1088-101.
58
59
60

- 1
2
3
4 22 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple,
5
6 graphical test. *BMJ* 1997;**315**:629-34.
7
8
9 23 Kellett SC, Gawkrödger DJ. The psychological and emotional impact of acne and the effect
10
11 of treatment with isotretinoin. *Br J Dermatol* 1999;**140**:273-82.
12
13
14 24 Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression,
15
16 psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* 2000;**136**:1231-6.
17
18
19 25 Ng CH, Tam MM, Celi E, et al. Prospective study of depressive symptoms and quality of
20
21 life in acne vulgaris patients treated with isotretinoin compared to antibiotic and topical
22
23 therapy. *Australas J Dermatol* 2002;**43**:262-8.
24
25
26 26 Ferahbas A, Turan MT, Esel E, et al. A pilot study evaluating anxiety and depressive scores
27
28 in acne patients treated with isotretinoin. *J Dermatolog Treat* 2004;**15**:153-7.
29
30
31 27 Chia CY, Lane W, Chibnall J, et al. Isotretinoin therapy and mood changes in adolescents
32
33 with moderate to severe acne: a cohort study. *Arch Dermatol* 2005;**141**:557-60.
34
35
36 28 Kellett SC, Gawkrödger DJ. A prospective study of the responsiveness of depression and
37
38 suicidal ideation in acne patients to different phases of isotretinoin therapy. *Eur J*
39
40 *Dermatol* 2005;**15**:484-8.
41
42
43 29 Kaymak Y, Kalay M, Ilter N, et al. Incidence of depression related to isotretinoin treatment
44
45 in 100 acne vulgaris patients. *Psychol Rep* 2006;**99**:897-906.
46
47
48 30 Cohen J, Adams S, Patten S. No association found between patients receiving isotretinoin
49
50 for acne and the development of depression in a Canadian prospective cohort. *Can J Clin*
51
52 *Pharmacol* 2007;**14**:e227-33.
53
54
55
56
57
58
59
60

- 1
2
3
4 31 Azoulay L, Blais L, Koren G, et al. Isotretinoin and the risk of depression in patients with
5
6
7 acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008;**69**:526-32.
8
9
10 32 Bozdag KE, Gulseren S, Guven F, et al. Evaluation of depressive symptoms in acne patients
11
12 treated with isotretinoin. *J Dermatolog Treat* 2009;**20**:293-6.
13
14
15 33 Kaymak Y, Taner E, Taner Y. Comparison of depression, anxiety and life quality in acne
16
17 vulgaris patients who were treated with either isotretinoin or topical agents. *Int J Dermatol*
18
19 2009;**48**:41-6.
20
21
22
23 34 Rehn LM, Meririnne E, Hook-Nikanne J, et al. Depressive symptoms and suicidal ideation
24
25 during isotretinoin treatment: a 12-week follow-up study of male Finnish military
26
27 conscripts. *J Eur Acad Dermatol Venereol* 2009;**23**:1294-7.
28
29
30
31 35 Simic D, Situm M, Letica E, et al. Psychological impact of isotretinoin treatment in patients
32
33 with moderate and severe acne. *Coll Antropol* 2009;**33 Suppl 2**:15-9.
34
35
36 36 McGrath EJ, Lovell CR, Gillison F, et al. A prospective trial of the effects of isotretinoin
37
38 on quality of life and depressive symptoms. *Br J Dermatol* 2010;**163**:1323-9.
39
40
41
42 37 Fakour Y, Noormohammadpour P, Ameri H, et al. The effect of isotretinoin (roaccutane)
43
44 therapy on depression and quality of life of patients with severe acne. *Iran J Psychiatry*
45
46 2014;**9**:237-40.
47
48
49
50 38 Ergun T, Seekin D, Ozaydin N, et al. Isotretinoin has no negative effect on attention,
51
52 executive function and mood. *J Eur Acad Dermatol Venereol* 2012;**26**:431-9.
53
54
55 39 Ormerod AD, Thind CK, Rice SA, et al. Influence of isotretinoin on hippocampal-based
56
57 learning in human subjects. *Psychopharmacology (Berl)* 2012;**221**:667-74.
58
59
60

- 1
2
3
4 40 Yesilova Y, Bez Y, Ari M, et al. Effects of isotretinoin on obsessive compulsive symptoms,
5
6 depression, and anxiety in patients with acne vulgaris. *J Dermatolog Treat* 2012;**23**:268-
7
8 71.
9
10
11
12 41 Marron SE, Tomas-Aragones L, Boira S. Anxiety, depression, quality of life and patient
13
14 satisfaction in acne patients treated with oral isotretinoin. *Acta Derm Venereol*
15
16 2013;**93**:701-6.
17
18
19
20 42 Gnanaraj P, Karthikeyan S, Narasimhan M, et al. Decrease in "Hamilton Rating Scale for
21
22 Depression" Following Isotretinoin Therapy in Acne: An Open-Label Prospective Study.
23
24 *Indian J Dermatol* 2015;**60**:461-4.
25
26
27
28 43 Suarez B, Serrano A, Cova Y, et al. Isotretinoin was not associated with depression or
29
30 anxiety: A twelve-week study. *World J Psychiatry* 2016;**6**:136-42.
31
32
33
34 44 Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with
35
36 isotretinoin: a systematic review. *Semin Cutan Med Surg* 2007;**26**:210-20.
37
38
39
40 45 Vallerand IA, Lewinson RT. Efficacy and adverse events of oral isotretinoin for acne: a
41
42 systematic review. 2017;
43
44
45 46 Huang YC, Cheng YC. Isotretinoin treatment for acne and risk of depression: A systematic
46
47 review and meta-analysis. *J Am Acad Dermatol* 2017;**76**:1068-76.e9.
48
49
50 47 Crandall J, Sakai Y, Zhang J, et al. 13-cis-retinoic acid suppresses hippocampal cell division
51
52 and hippocampal-dependent learning in mice. *Proc Natl Acad Sci U S A* 2004;**101**:5111-
53
54 6.
55
56
57
58 48 Bremner JD, Fani N, Ashraf A, et al. Functional brain imaging alterations in acne patients
59
60

- 1
2
3
4 treated with isotretinoin. *Am J Psychiatry* 2005;**162**:983-91.
5
6
7 49 O'Reilly KC, Trent S, Bailey SJ, et al. 13-cis-Retinoic acid alters intracellular serotonin,
8
9 increases 5-HT1A receptor, and serotonin reuptake transporter levels in vitro. *Exp Biol*
10
11
12 *Med (Maywood)* 2007;**232**:1195-203.
13
14
15 50 Misery L. Consequences of psychological distress in adolescents with acne. *J Invest*
16
17 *Dermatol* 2011;**131**:290-2.
18
19
20 51 Aktan S, Ozmen E, Sanli B. Anxiety, depression, and nature of acne vulgaris in adolescents.
21
22
23 *Int J Dermatol* 2000;**39**:354-7.
24
25
26 52 Yang YC, Tu HP, Hong CH. Female gender and acne disease are jointly and independently
27
28 associated with the risk of major depression and suicide: a national population-based study.
29
30
31 *BioMed Research International* 2014;**2014**:504279.
32
33
34 53 Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and
35
36 psychological morbidity in mid-adolescence: a community-based study. *Br J Dermatol*
37
38
39 2001;**145**:274-9.
40
41
42 54 Thiboutot D, Dreno B, Layton A. Acne counseling to improve adherence. *Cutis* 2008;**81**:81-
43
44
45 6.
46
47
48 55 Hansen TJ, Lucking S, Miller JJ, et al. Standardized laboratory monitoring with use of
49
50 isotretinoin in acne. *J Am Acad Dermatol* 2016;**75**:323-8.
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Table 1. Characteristics of included studies

Author (year)	Region	Design	Isotretinoin users	Mean/Median age (year)	Female (%)	Acne severity	Comparison groups	Dose	Treatment duration	Depression assessment
Kellett et al. (1999)	UK	Prospective	34	24	44	NA	Before vs after	1.0 mg/(kg · d)	4 months	HADS-D
Pick et al. (2000) a	Canada	Retrospective	7195	<30 (75%)	47	NA	Before vs after	40 mg (86%)	3–6 months (62%)	ICD code
Pick et al. (2000) b	UK	Retrospective	340	<30 (78%)	42	NA	Before vs after	20 mg (75%)	1–2 months (81%)	ICD code
Ng et al. (2002)	Australia	Prospective	174	20	41	Moderate to severe	Before vs after	0.8–1.0 mg/(kg · d)	6 months	BDI

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Ferahbas et al. (2004)	Turkey	Prospective	23	20	43	Severe	Before vs after	0.5–1.0 mg/(kg · d)	4 months	MADRS
Kellett et al. (2005)	UK	Prospective	33	25	36	NA	Before vs after	1.0 mg/(kg · d)	4 months	BDI
Kaymak et al. (2006)	Turkey	Prospective	24	100	58	Moderate	Before vs after	0.75–1.0 mg/(kg · d)	5–7 months	HRS
Chia et al. (2005)	USA	Prospective	59	12–19	25	Moderate to severe	Before vs after	1.0 mg/(kg · d)	3–4 months	CES-D
Azoulay et al. (2008)	Canada	Retrospective	126	28	53	NA	Users vs nonusers	NA	5 months	ICD code
Kaymak et al. (2009)	Turkey	Prospective	37	21	69	Mild to severe	Before vs after	0.5–0.8 mg/(kg · d)	> 5 months	BDI, HADS-D

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Bozdag et al. (2009)	Turkey	Prospective	50	20	52	Moderate	Before vs after	1.0 mg/(kg · d)	4 months	BDI
							to severe			
Rehn et al. (2009)	Finland	Prospective	126	20	0	Moderate	Before vs after	0.5 mg/(kg · d)	3 months	BDI
							to severe			
Simic et al. (2009)	Bosnia and Herzegovina	Prospective	85	19	34	Moderate	Isotretinoin vs vitamin C	1.0 mg/(kg · d)	2 months	BDI
							to severe			
McGrath et al. (2010)	UK	Prospective	65	20	31	Mean	Before vs after	0.5–1.0 mg/(kg · d)	3 months	CES-D
							AGS			
							score 3.3			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Ergun et al. (2012)	Turkey	Prospective	65	22	73	Severe or resistant	Before vs after	0.5–1.0 mg/(kg · d)	≈ 5 months	HADS-D
Ormerod et al. (2012)	UK	Prospective	16	22	25	Severe	Before vs after	0.5–1.0 mg/(kg · d)	3–6 months	BDI
Yesilova et al. (2012)	Turkey	Prospective	43	23	70	Mild to severe	Before vs after	0.5–1.0 mg/(kg · d)	6 months	HADS-D
Marron et al. (2013)	Spain	Prospective	346	21	59	Moderate	Before vs after	Total: 120 mg/kg	7 months	HADS-D
Fakour et al. (2014)	Iran	Prospective	98	22	61	Severe	Before vs after	0.5 mg/(kg · d)	4 months	BDI
Gnanaraj et al. (2015)	India	Prospective	143	21	34	Moderate to severe	Before vs after	0.5 mg/(kg · d)	3 months	HRS

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Suarez et al. (2016)	Venezuela	Prospective	36	21	44	Severe	Before vs after	30 mg/d	3 months	ZDS
						(25%)				

AGS, Acne grading scale; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; ICD, International Classification of Diseases; MADRS, Montgomery–Asberg depression rating scale; NA, not available; ZDS, Zung self-rating depression scale.

Table 2. Subgroup analysis for studies presenting depressive symptom scores after isotretinoin compared with the baseline

Subgroups	Number of cohorts	SMD (95% CI)	<i>P</i> value	<i>I</i> ² (<i>P</i> value)
Region				
Europe	14	−0.35 (−0.51 to −0.19)	<0.05	46.3% (<0.05)
Asia	3	−0.18 (−0.81 to 0.45)	0.57	94.4% (<0.05)
North America	1	−0.23 (−0.59 to 0.13)	0.21	–
Africa	1	−0.74 (−1.22 to −0.26)	<0.05	–
Depression scale				
BDI	10	0.10 (−0.12 to 0.32)	0.38	65.2% (<0.05)
HADS-D	4	0.57 (0.31–0.83)	<0.05	27.2% (0.25)
CES-D	2	0.27 (0.02–0.52)	<0.05	0% (0.78)
HRS	2	0.55 (−0.46 to 1.56)	0.29	96.6% (<0.05)
MADRS	1	0.33 (−0.25 to 0.91)	0.27	–
ZDS	1	0.74 (0.26–1.22)	<0.05	–
Sample size				

1					
2					
3					
4	<50	9	-0.38 (-0.65 to -0.12)	<0.05	64.0% (<0.05)
5					
6					
7	≥50	11	-0.29 (-0.54 to -0.04)	<0.05	83.1% (<0.05)
8					
9					
10					
11	Percentage of female patients				
12					
13					
14	<50	12	-0.32 (-0.55 to -0.09)	<0.05	76.8% (<0.05)
15					
16					
17					
18	≥50	8	-0.34 (-0.04 to -0.64)	<0.05	78.4% (<0.05)
19					
20					

BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression

Scale; CI, confidence interval; HADS-D, hospital anxiety and depression scale-depression;

HRS, Hamilton Rating Scale; MADRS, Montgomery–Asberg depression rating scale; SMD,

standardized mean difference; ZDS, Zung self-rating depression scale.

1
2
3
4 **Figure legends:**
5

6 **Figure 1.** Study selection process.
7

8
9 **Figure 2.** Forest plot showing the standardized mean difference for the comparison of
10 depression symptom scores before and after isotretinoin treatment in patients with acne.
11
12

13
14 **Figure 3.** Funnel plot of studies comparing depression symptom scores before and after
15 isotretinoin treatment in patients with acne.
16
17

18
19 **Figure 4.** Forest plot showing the weighted mean difference for the comparison of BDI scores
20 before and after isotretinoin treatment in patients with acne.
21
22

23
24 **Figure 5.** Forest plot showing the association between isotretinoin treatment and depression in
25 patients with acne.
26
27

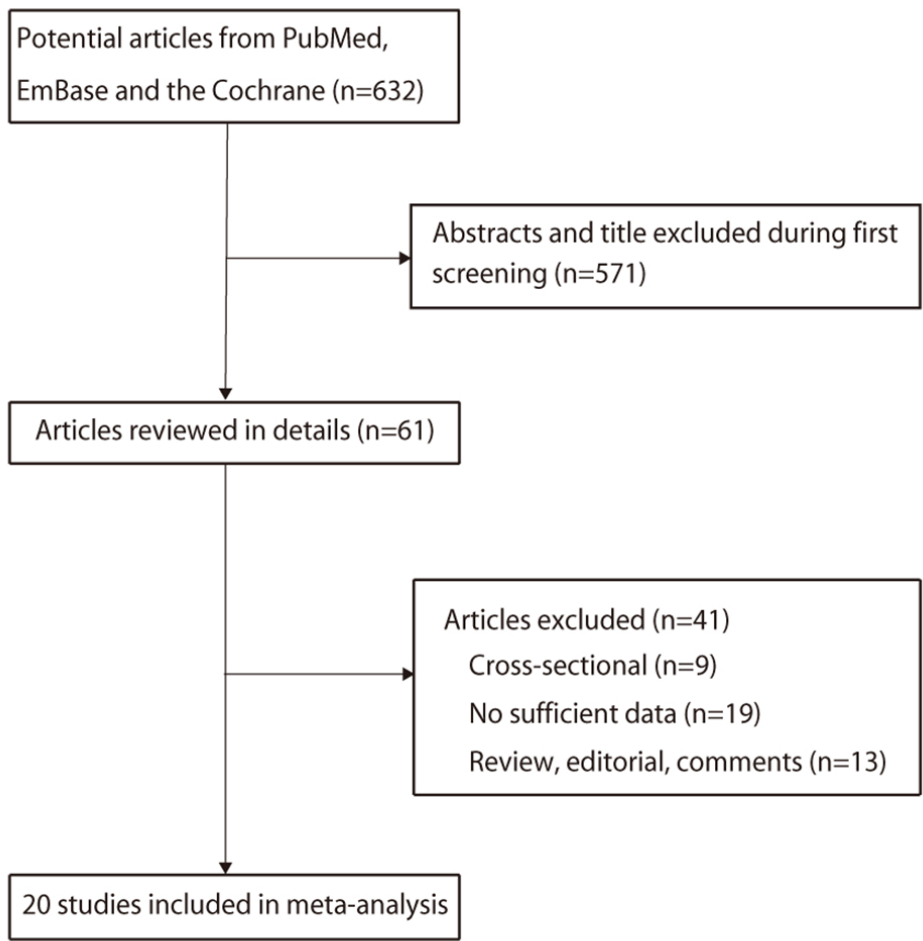
28
29 **Figure 6.** Funnel plot showing the association between isotretinoin treatment and depression
30 in patients with acne.
31
32

33
34
35
36
37
38
39 **Legends for supporting information**
40

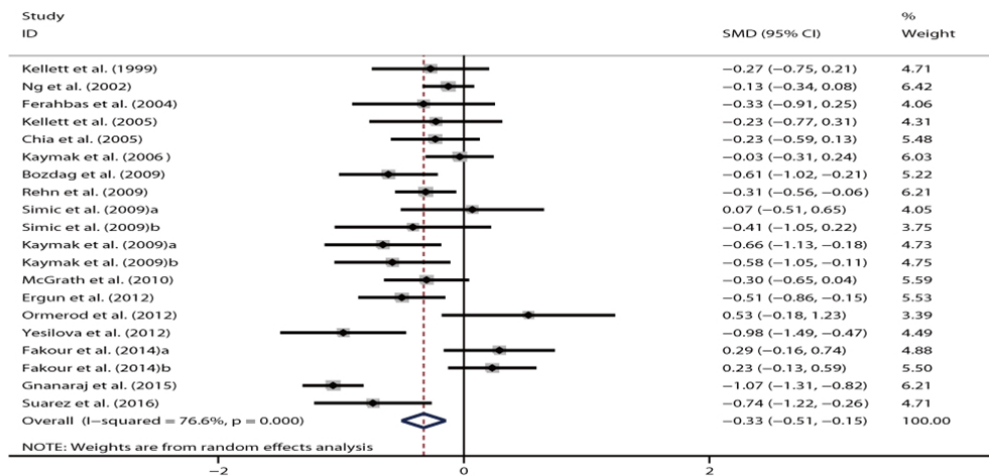
41
42 **Supplemental 1.** The details of searching strategy in PubMed.
43

44
45 **Supplemental 2.** Newcastle–Ottawa Scale for quality assessment of included studies
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

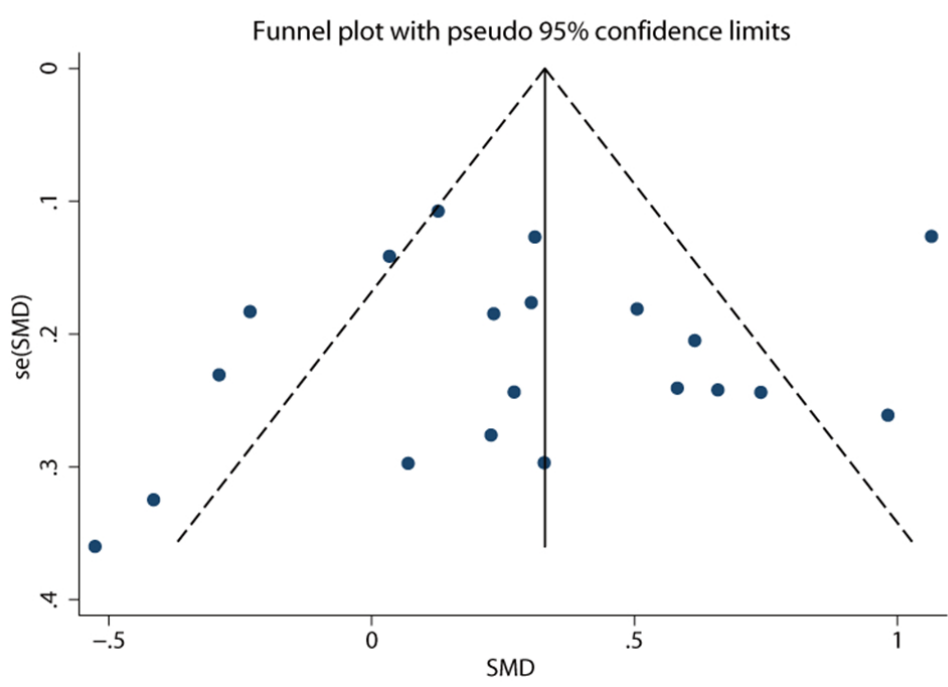
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



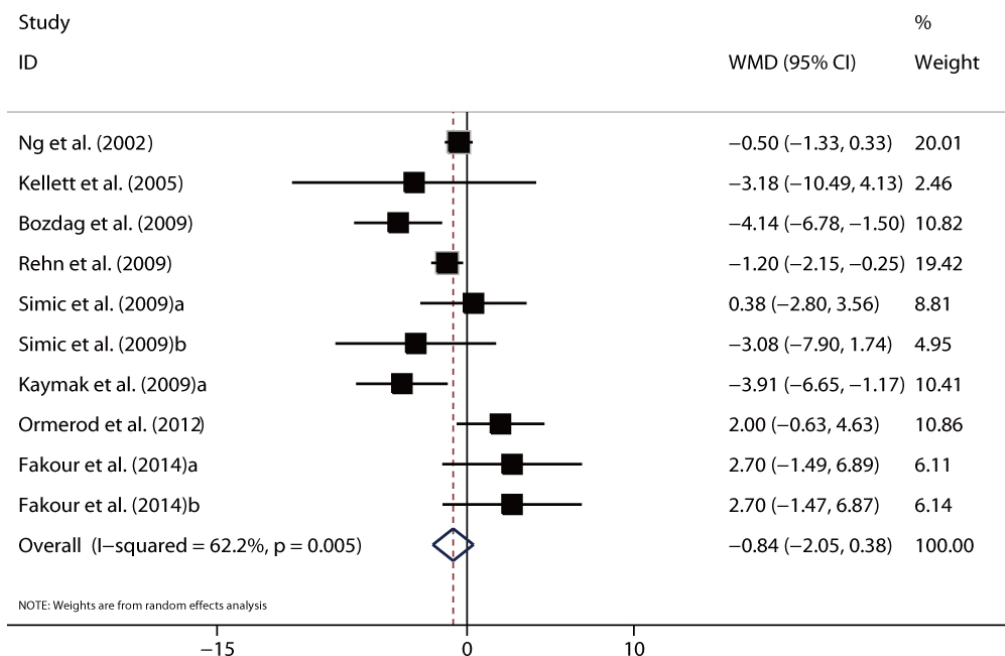
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

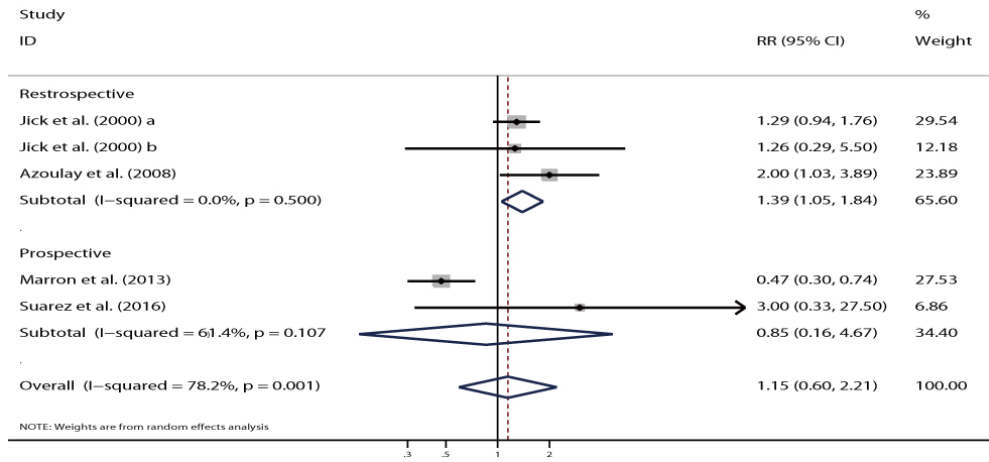


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

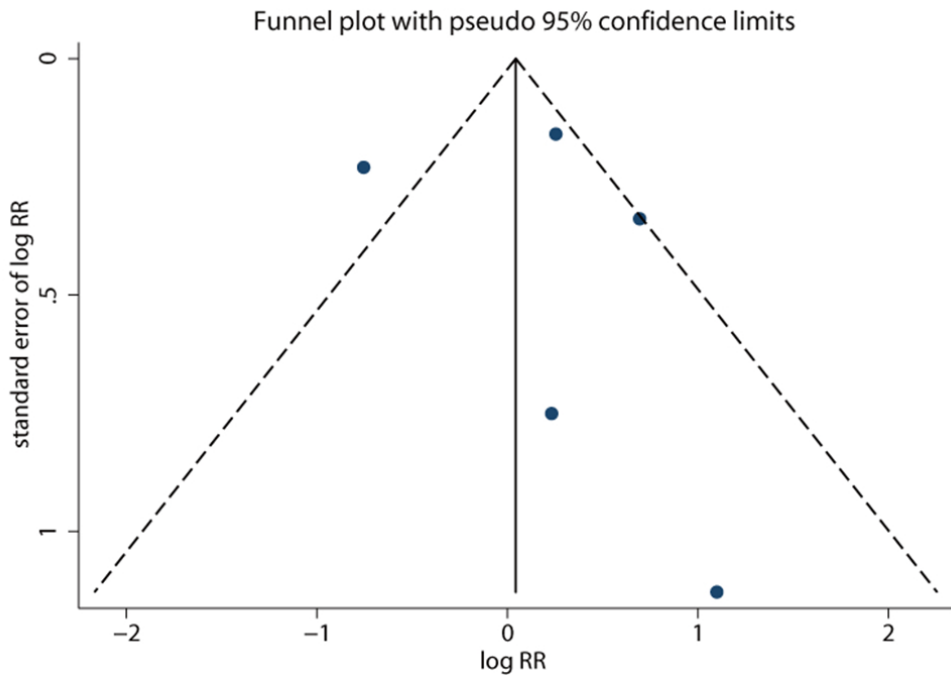


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60





1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Searching strategy in PubMed:

((("depression"[Mesh] OR "depression") OR "depressive"[Mesh] OR "depressive") AND ("acne"[Mesh] OR "acne") AND ("isotretinoin"[Mesh] OR "isotretinoin"))

For peer review only

1
2
3
4 **Use of isotretinoin and risk of depression in patients with acne: a systematic**
5
6 **review and meta-analysis**
7

8
9 Changqiang Li², Jianmei Chen¹, Wo Wang³, Ming Ai¹, Qi Zhang¹, Li Kuang^{1*}
10

11
12 ¹Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical
13
14 University, Chongqing 400016, China
15

16
17 ²Department of Dermatology, The Affiliated Hospital of Southwest Medical
18
19 University, Luzhou , 646000, China
20

21
22 ³Mental Health Center, University-Town Hospital of Chongqing Medical University,
23
24 Chongqing 401331, China
25

26
27
28
29
30 *Corresponding author:
31

32
33 Li Kuang
34

35
36 Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical
37
38 University, Chongqing 400016, China
39

40
41 Tel: +86-13908379733
42

43
44 Fax: +86-21-64085875
45

46
47 Email: kuangli0308120@126.com
48
49
50
51
52
53
54
55
56
57
58
59
60

Supplemental Table 1. Newcastle–Ottawa scale for quality assessment of included studies

Study	Selection	Comparability	Outcome
Kellett et al. (1999)	****	*	***
Jick et al. (2000) a	****	**	**
Jick et al. (2000) b	****	**	**
Ng et al. (2002)	****	*	***
Ferahbas et al. (2004)	****	*	***
Kellett et al. (2005)	****	*	***
Kaymak et al. (2006)	****	*	***
Chia et al. (2005)	***	*	***
Azoulay et al. (2008)	****	**	**
Kaymak et al. (2009)	****	*	***
Bozdag et al. (2009)	****	*	***
Rehn et al. (2009)	***	*	***
Simic et al. (2009)	****	*	***
McGrath et al. (2010)	****	*	***
Ergun et al. (2012)	****	*	***
Ormerod et al. (2012)	***	*	***
Yesilova et al. (2012)	****	*	***
Marron et al. (2013)	****	*	***
Fakour et al. (2014)	****	*	***
Gnanaraj et al. (2015)	****	*	***
Suarez et al. (2016)	****	*	***



PRISMA 2009 Checklist

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS and length of follow-up) and report characteristics (e.g., years considered, language, and publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage and contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS and funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio and difference in means).	4–5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4–5



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias and selective reporting within studies).	4–5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses and meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, and follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	6–7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6–7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6–7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses and meta-regression [see Item 16]).	6–7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	7–9
Limitations	25	Discuss limitations at study and outcome levels (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research and reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>