

1 **Appendix Hoofdstuk 9: Wetenschappelijke onderbouwing**
 2 **elektroconvulsie therapie**

3 In making their recommendations, the GDG considered the results of several
 4 previous reviews identified through the search for evidence. These reviews were

5 **9.1.2 Clinical review protocol**

Topic	Interventions
Review question(s)	RQ: For adults with (treatment resistant) bipolar disorder, what are the relative benefits and harms of electroconvulsive therapy (ECT)?
Sub-question(s)	Does the effectiveness of treatment vary for: People in a depressed, manic or mixed state? 2. Adults (18 to 64) and older adults (65+). What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) people of different genders?
Objectives	To estimate the efficacy of ECT to treat mania, mixed state and depression in bipolar disorder
Criteria for considering studies for the review	
Intervention	Electroconvulsive therapy
Comparator	Placebo, Treatment as usual (medication), Waitinglist, Other interventions
Types of participants	Adults (18+) with bipolar disorder who are treatment resistant. Special consideration will be given to the groups above.
Outcomes	1. Change in symptoms of mania 2. Change in symptoms of depression 3. Response 4. Relapse 5. Switching (all, to mania/mixed, to depression) 6. Discontinuation (due to side effect) 7. Mortality (all cause, suicide attempts, suicides completed)

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Time	The analysis will include outcomes at the end of the treatment phase and after a follow-up periode.
Study design	(Quasi-)Randomised controlled trials (RCTs), prospective comparative trials and prospectieve case series, with a minimum of 12 participants. Also systematic reviews will be included.
Dosage	ECT can be delivered unilateral, bilateral or bifrontal. These differences will not be the subject of our review.
Study country	Primary, secondary, tertiary, health and social care.
Search strategy	<p>Searches for trials on the use of electroconvulsive therapy in persons with bipolar disorder were conducted in PsycInfo, PubMed, CINAHL en Cochrane-library.</p> <p>PubMed</p> <p>The following MESH terms were used in PubMed: 'Electroconvulsive Therapy [Mesh:NoExp]' and 'electroconvulsive shock therapy' OR 'electroconvulsive therapy' in the title. Combined with the MESH term 'Bipolar Disorder'[Mesh:NoExp] and 'bipolar disorder*' in title.</p> <p>PsycInfo</p> <p>The thesaurus terms used in PsycInfo are 'Bipolar Disorder' and 'Electroconvulsive Shock Therapy'.</p> <p>CINAHL</p> <p>The same thesaurus terms were used as in PubMed.</p> <p>Cochrane-library</p> <p>In de Cochrane database a search was conducted with a combination of 'bipolar disorder*' and 'electroconvulsive' in the title.</p> <p>The searches were conducted on the 19th of July 2013 and references lists of the included studies were cross-referenced.</p>
Study design filter/limit used	<p>There is were no restriction placed on year of publication or language</p> <p>We searched by limiting to 'human' population. PsycINFO was limited to 'Adulthood (18 yrs & older) and in PubMed to "Adult: 19 + years".</p>
Question specific search strategy	No

Amendments to search strategy/study design filter	None
Searching other resources	No
The review strategy	<p>The reviewer will conduct the search. A GDG member will undertake the first (on title and abstract) and the second selection (on full text). When selecting the full text articles it is important that the following criteria are clearly marked in the paper: 1. Design; 2. Outcomes; 3. Patient group size; 4. Method/technical parameters of ECT. Studies will be excluded with the help of the earlier described "Criteria for considering studies for the review". Serious doubt about in- or exclusion of studies will be discussed between GDG-member and reviewer.</p> <p>If reviews are found, they will also be selected as described. The studies in the review will not be extracted separately.</p> <p>Data extraction and RoB assessment of individual studies and/or reviews will be done by the reviewer with the help of templates. The quality of the body of evidence will be judged with GRADE.</p>

1 Included and excluded studies

2 In our search we found 179 articles in PsycInfo, 578 articles in PubMed and 59 in
 3 CINAHL. In the Cochrane database we found one review. Of these articles 122
 4 were double references. We were finally left with 695 articles.

5 Of 695 potentially relevant citations, we retrieved 30 papers (28 from the search
 6 and two cross referenced). Of these, eight were review articles of which five
 7 were excluded because of methodological flaws and one because it was a
 8 summary of a report (Greenhalgh2005). Reason for exclusion of the reviews
 9 (Keck2000, Mukherjee1989, Mukherjee1994, Vaidya2003) was that the method
 10 of the search, selection procedure and measurements were not adequately
 11 described, hampering assessment of quality for these studies. Of the other 22
 12 citations, 12 were excluded as they did not meet our "Criteria for considering
 13 studies for the review". The other ten could be excluded because these citations
 14 were also included in the three reviews (Loo2011, Versiani2011 and
 15 Valenti2008).

16 *Results*

17 The reviews described results from studies with different methodological quality
 18 in their designs. Per bipolar state (mania, depression and mixed) only data from
 19 the reviews were extracted of studies with the lowest risk of bias. In the

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- 1 evidence table (Table 1), more information on the study characteristics and
- 2 methodological quality of the systematic reviews can be found.
- 3 **Table 1:** Evidence table of systematic reviews of ECT studies in bipolar disorder

Reference: Valenti M, Benabarre A, Garcia-Amador M, Molina O, Bernardo M, Vieta E. Electroconvulsive therapy in the treatment of mixed states in bipolar disorder. Eur Psychiatry 2008; 23(1):53-56.	
Methods	Study aim: The objective of this systematic review was to analyze the evidence base supporting the use of ECT in bipolar mixed states. Study design: prospective clinical trials Analysis: descriptive
Patients	Number of studies: k= 3 (1 which included enough patients, Ciapparelli et al.) Number of patients: n= 58 (41 in the included study, Ciapparelli et al.) Age: - Sex: - Inclusion: (1) prospective clinical trials, (2) English language, (3) mixed states treated with electroconvulsive therapy, (4) published between March 1992 and March 2007, (5) including adult patients, (6) including more than five patients, (7) including standardized diagnostic criteria, such as DSM, ICD, or RDC, (8) including standardized evaluation criteria, such as MADRS, BPRS, CGI-S and SADS-C. Exclusion: - Baseline characteristics: -
Interventions	Intervention: ECT Control: -

	Follow-up time: -
Outcome	<p>Primary: Ciapparelli et al.:</p> <p>Subjects were evaluated using the Montgomerye Asberg Depression Rating Scale (MADRS), the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impressions-Severity of Illness scale (CGI-S).</p> <p>Secondary: -</p> <p>Results of included studies for the guideline are presented in table 1.</p>
Quality Assessment	<p>Study question: + The objective of this systematic review was to analyze the evidence base supporting the use of ECT in bipolar mixed states.</p> <p>Search strategy: +/- The MEDLINE database was scrutinized in order to conduct a comprehensive and objective review of the literature on the treatment of mixed states, focusing on electroconvulsive therapy.</p> <p>Selection process: + The articles were selected if they met the certain criteria</p> <p>Quality assessment: + prospective clinical trials</p> <p>Data extraction: ?</p> <p>Characteristics original studies: +</p> <p>Handling heterogeneity: ?</p> <p>Statistical pooling: ?</p> <p>Funding / conflicts of interest: ?</p> <p>Overall quality of evidence: - / ?</p> <p>General conclusion: + /-</p>

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Reference: Loo C, Katalinic N, Mitchell PB, Greenberg B. Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. J Affect Disord 2011; 132(1-2): 1-13.

Methods	<p>Study aim: This article reviews the evidence base for the use of electroconvulsive therapy (ECT) and other brain stimulation therapies in bipolar disorder.</p> <p>Study design: All types of studies (e.g., retrospective chart reviews; prospective studies; doubleblind, randomized controlled trials; open-label uncontrolled studies; naturalistic observations; case reports; case series; register-based case-controlled studies) and formats (research reports, brief reports, review articles, meta-analyses, poster presentations, letters to the editor, commentaries, correspondence, intellectual publications, editorials) as well as reviewing practice guidelines published in English over the last decade.</p> <p>Blinding: -</p> <p>Analysis: Qualitative and narrative review</p> <p>Duration of the study: searched up to May 2010</p> <p>Setting/Location: Inclusion criteria of being written in the English language, of including patients with bipolar disorder, and of being published in a peer-reviewed journal.</p>
Patients	<p>Number of studies: Not clearly reported</p> <p>Number of patients: Not clearly reported</p> <p>Age: Adult</p> <p>Sex: -</p> <p>Inclusion: All bipolar patients</p> <p>Exclusion: -</p> <p>Baseline characteristics: -</p>
Interventions	<p>Intervention: Electroconvulsive therapy</p> <p>Control: sham ECT, other types of ECT, medication</p> <p>Follow-up time: -</p>
Outcome	<p>Primary: Recovery</p> <p>Secondary: all types</p> <p>Results of included studies for the guideline are presented in table 1.</p>
Quality Assessment	<p>Study question: +/-</p> <p>Search: +</p> <p>Selection: +</p> <p>Quality assessment: ? Unclear</p>

	<p>Data extraction: ?</p> <p>Description of original studies: ?</p> <p>Handling heterogeneity: -</p> <p>Statistical pooling: - (not possible)</p> <p>Funding / conflicts of interest: -</p> <p>Quality of evidence: +/-</p> <p>General conclusion: Although the review is narrative, the search and selection is clearly described. It includes some studies the other two reviews for the guideline do not, so it's useful to include this review. But results should be handled with caution.</p>
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<p>Reference: Versiani M, Cheniaux E, Landeira-Fernandez J. Efficacy and safety of electroconvulsive therapy in the treatment of bipolar disorder: a systematic review. J ECT 2011; 27(2):153-164.</p>	
Methods	<p>Study aim: To evaluate the efficacy and safety of electroconvulsive therapy (ECT) in bipolar disorder (BPD).</p> <p>Study design: systematic review of clinical trials</p> <p>Analysis: descriptive</p> <p>Setting: hospital</p>
Patients	<p>Number of studies: k= a total of 51 articles met our selection criteria. Only 3 controlled or comparative prospective trials addressed the treatment of mania with ECT.</p> <p>Number of patients: -</p> <p>Age: -</p> <p>Sex: -</p> <p>Inclusion: All studies with a sample of at least 10 patients with BPD treated with ECT were selected. For the purpose of the present review, the diagnosis of schizoaffective disorder (bipolar type) was considered a form of BPD, which is coherent with the view that schizoaffective disorder does not represent a distinct nosological entity</p> <p>Exclusion: -</p> <p>Baseline characteristics: in episode</p>

Interventions	<p>Intervention: ECT</p> <p>Control: simulated ECT, lithium, the combination of lithium and Haloperidol, antidepressants</p> <p>Follow-up time:</p>
Outcome	<p>Primary: Patient improvement, discharged to home and Safety</p> <p>Secondary: -</p> <p>Results of included studies for the guideline are presented in table 1.</p>
Quality Assessment	<p>Study question: +</p> <p>Search strategy: + MEDLINE, PsycINFO, and ISI Web of Science databases, up to March 25, 2010</p> <p>Selection process: + Two of the authors screened all of the abstracts and made a decision concerning the importance of the work. [Good in and exclusion criteria]</p> <p>Quality assessment: +/-, did look at the type of study (RCT or not) and partly at the quality of the RCT's (blinded or not)</p> <p>Data extraction: +</p> <p>Characteristics original studies: +</p> <p>Handling heterogeneity: ?</p> <p>Statistical pooling: -</p> <p>Funding / conflicts of interest: + / - / ?</p> <p>Overall quality of evidence: + / - / ?</p> <p>General conclusion: +</p>

1 Mania

2 Versiani2011 and Loo2011 both found the same three RCT's, including 91
 3 patients in total. Only one trial (Sikdar et al. 1994) was double blinded, the
 4 other two were not blinded (Small et al. 1988; Mukherjee et al. 1989).

5 In two studies recovery from mania was an outcome measure. Sikdar et al.
 6 (1994) compared ECT vs sham ECT (15 patients in each group) and Mukherjee
 7 et al. (1989) ECT vs lithium and haloperidol (22 and 5 treatment resistant
 8 patients respectively), resulting in respectively 12 vs 1 recovered (scores below 6
 9 on Mania Rating Scale for at least one week) and 13 vs 0 patients that recovered
 10 (not meeting RDC (Research diagnostic criteria) for a manic episode for seven
 11 days). In the Small et al. (1988) study, which compared ECT vs Lithium (n=17
 12 vs n=17), continuous measurements were used. Only on the Clinical Global
 13 Impression and Global Assessment Scales there was a slight advantage for ECT

1 but not on the Brief Psychiatric Rating Scale (BPRS) and Bech-Rafaelsen Manic
2 Rating Scale (BR-MRS), although within the ECT-group there was a significant
3 reduction on the BR-MRS.

4 Depression

5 Loo2011 found one double blind RCT (Greenblatt et al. (1964)) with four arms,
6 which included recently hospitalized patients with bipolar disorder. When the ECT
7 arm (n=63) was compared with the antidepressant arm (n=73) there was a
8 statistically significant improvement in recovery (78% vs 59%). Also, ECT led to
9 superior outcomes in global clinical ratings, depression ratings, and behavioural
10 measures.

11 Mixed

12 Loo2011, Valenti2008 and Versiani2011 found in total two non-comparative
13 prospective trials (Ciapparelli et al. (2001); Medda et al. (2010)). Both studies
14 included participants who were non responsive to medication, but continued
15 using medication during ECT. In the Ciapparelli et al. (2001) study 56% of 41
16 participants responded (measured with the CGI) after ECT and in the Medda et
17 al. (2010) it was 76% of the 50 participants. Both studies found that general
18 psychopathology and activation (Brief Psychiatric Rating Scale, BPRS) improved
19 substantially. Ciapparelli et al. (2001) found that ECT was highly effective in
20 reducing suicidal ideation and Medda et al. (2010) found improvements on
21 mania (YMRS) and depression symptoms (HAM-D).

22 Safety

23 Loo 2011 found two studies (Angst et al. (1992); (Henry et al., 2001)) reporting
24 on switching to mania after ECT in bipolar depression. In a small comparative
25 prospective study (n=44) switching events were compared in periods of ECT
26 treatment and when taking antidepressants. (Henry et al., 2001) In the group
27 receiving ECT 36% switched and in the group taking antidepressants 24%
28 switched. In a larger study Angst et al. (1992) 1057 hospital admissions of
29 (bipolar) depressed patients were reviewed. In the study they compared
30 switching events in periods of ECT treatment, when taking antidepressants and
31 also in periods without treatment. Differences in switching for patients with
32 bipolar disorder were not significant (28.6% with no treatment, 37.5% with ECT
33 and 29.5% with antidepressants). Because of the retrospective nature of the
34 study and because some participants received antidepressants directly after ECT,
35 results should be interpreted with caution.

36 Versiani2011 found three prospective trials (MacQueen et al. (2007); Small et al.
37 (1986); Cohen et al. (2000)) comparing ECT with medication on cognitive
38 outcomes. Small et al. (1986) found in their RCT no differences on general
39 intelligence (Wechsler Adult Intelligence Scale (WAIS)) between the group which
40 had received ECT (N=10) or Lithium (n=11). In the Cohen et al. (2000) study no

1 differences were found on cognitive scales (Mini-mental state examination
2 (MMSE), Weschler Memory Scale (WMS), California Verbal Learning Test (CVLT))
3 between the ECT (n=10) and medication group (n=10). But, in the MacQueen et
4 al. (2007) only one cognitive scale (Continuous Visual Memory Test (CVMT))
5 showed no differences between the two groups (N=20 vs 20), the other two
6 scales (Cognitive Failures Questionnaire (CFQ) and CVLT) were in favor of the
7 medicated group. When the two groups were compared with a normal control
8 group (N=20), the ECT and medicated group showed more memory complaints
9 (CFQ) and worse performance on the CVLT (verbal learning and memory).

10 **9.1.3 Overige studies**

11 Indien de bovenstaande review wordt uitgebreid met studies die aan
12 methodologisch minder strikte eisen voldoen wordt aanvullende evidentie
13 verkregen over de effectiviteit van ECT bij bipolaire stoornissen. De werkgroep
14 heeft de onderstaande studies meegewogen vanwege het beperkte aantal
15 studies dat aan de strikte methodologische criteria voldeed. Alle gepubliceerde
16 studies die de effectiviteit van ECT onderzochten laten zien dat ECT effectief
17 was, waarbij de symptomen (manisch, gemengd of depressief) verminderden of
18 de patiënt volledig herstelde. Nadat halverwege de 20e eeuw werd aangetoond
19 dat ECT effectiever was dan sham-ECT zijn er nog maar enkele RCT's uitgevoerd
20 met ECT. Hierdoor wordt op basis van de huidige literatuur geconcludeerd dat de
21 wetenschappelijke evidentie voor de effectiviteit van ECT van zeer lage graad is.

22 Manie

23 Versiani vond 28 studies die ECT onderzochten bij de bipolaire manie (Versiani
24 et al 2011). Er waren 14 niet-vergelijkende retrospectieve studies, waarvan 10
25 uit de jaren 40 toen er nog geen medicatie beschikbaar was. In deze studies
26 werd in 48.1 tot 100% van de patiënten een verbetering van klinisch beeld
27 gevonden. Er waren 5 niet-vergelijkende prospectieve studies die ook een
28 klinische verbetering vonden bij 64.3 tot 92% van de patiënten. In 3 van de 4
29 vergelijkende retrospectieve studies wordt gevonden dat de opnameduur van
30 manische patiënten behandeld met ECT niet korter is vergeleken met manische
31 patiënten behandeld met medicatie, wel was ECT effectiever dan medicatie
32 (Versiani et al 2011).

33 Er waren 2 gecontroleerde retrospectieve studies, bij Schiele en Schneider was
34 de opnameduur gelijk voor ECT behandelde en onbehandelde manische
35 patiënten (Schiele en Schneider 1949), maar McCabe vond een significant
36 klinisch herstel dat bovendien leidde tot een significant korter opnameduur
37 (McCabe 1976).

38 Er waren 2 vergelijkende prospectieve studies (Mukherjee 1989, Small et al
39 1988). Small et al vergeleek ECT met lithium (n=17 in ieder groep), algemeen
40 klinische en manische symptomen (gemeten met CGI en BR-MRS) verbeterden
41 significant meer in ECT groep (Small et al 1988). Als ECT (n=22) vergeleken

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1 wordt met lithium en haloperidol (n=5) zijn er 59% patiënten die herstellen van
2 de manische symptomen na ECT tegen 0% in de medicatiegroep (Mukherjee
3 1989).

4 Er is maar 1 gecontroleerde prospectieve studie die ECT met chloorpromazine
5 (n=15) vergelijkt met sham-ECT met chloorpromazine (n=15) (Sikdar et al
6 1994), waarbij ECT een superieure response heeft (12 vs 1).

7 Van de 28 studies die ECT bij de behandeling van manie onderzochten zijn er
8 maar 3 gecontroleerde of vergelijkende prospectieve studies, in deze studies is
9 er een betere klinische response bij ECT dan bij sham ECT (Sikdar 1994), lithium
10 (Small 1988) of lithium-haloperidol combinatie (Mukherjee 1989), maar de
11 methodiek van deze studies is zwak. Alle 28 studies tonen aan dat ECT effectief
12 kan zijn bij de behandeling van manie.

13 Gemengde episode

14 Er zijn 4 studies gevonden die de effectiviteit van ECT in de gemengde episode
15 onderzochten. Medda onderzocht ECT in 50 therapieresistente patiënten met een
16 gemengde episode (Medda et al 2010), met uitzondering van anticonvulsiva
17 werd medicatie gecontinueerd tijdens de ECT kuur. Er was een klinische
18 response in 76% van de patiënten, gemeten met CGI, en een significante
19 afname van manische (YMRS) en depressieve (HAM-D) symptomen. Ciapparelli
20 vergeleek ECT in patiënten met een gemengde en depressieve episode
21 (Ciapparelli et al 2001). Alle patiënten waren therapieresistent en bleven
22 medicatie gebruiken tijdens de ECT kuur. Er was een klinische response in 56%
23 van de 41 patiënten met een gemengde episode, er was een significante grotere
24 afname van suicidaliteit in de patiënten met gemengde episode. Devanand
25 vergeleek ECT in bipolaire depressie, manie en gemengde episode, 80% van de
26 10 patiënten met een gemengde episode had een klinische verbetering (CGI-S),
27 dit was vergelijkbaar met de andere groepen maar patiënten met een gemengde
28 episode hadden gemiddeld meer ECT behandelingen nodig met een langere
29 opnameduur (Devanand et al 2000). Gruber vond dat alle 7 therapieresistente
30 patiënten met een gemengde episode herstelden met ECT (SADS-C).

31 Er zijn maar 4 studies zijn die ECT bij patiënten met een gemengde episode
32 onderzochten, alle patiënten waren therapieresistent. Alle 4 studies tonen aan
33 dat ECT effectief is in het verminderen van symptomen van een gemengde
34 episode.

35 Bipolaire depressie

36 Er is maar 1 dubbelblinde RCT die de behandeling van een bipolaire depressie
37 met ECT onderzocht. Er waren 5 armen; ECT (n=63), imipramine (n=73),
38 phenelzine (n=38) monoamine oxidase remmer (n=68) en placebo (n=39). ECT
39 response (76%) was significant beter dan placebo (46%) of medicatie (28-
40 50%).

1 Recente reviews vonden 9 (Versiani et al 2011) en 7 (Loo et al 2011) klinische
2 onderzoeken naar ECT bij bipolaire depressie en 10 (Versiani et al) en 11 (Loo et
3 al 2011) klinisch studies die ECT behandeling van unipolaire vergeleken met
4 bipolaire depressie, dit betreffen vergelijkende retrospectieve of niet-
5 vergelijkende prospectieve en retrospectieve studies. Er lijkt weinig
6 wetenschappelijk aandacht voor de behandeling van de bipolaire depressie in
7 contrast met de onderzochte effectiviteit van ECT bij de unipolaire depressie. De
8 meeste studies vergelijken ECT met een behandeling met tricyclische
9 antidepressiva of monoamine oxidase remmers, waarbij patiënten vaker
10 verbeteren of herstellen na ECT, alhoewel dit verschil niet altijd significant is
11 (Loo et al 2011, Versiani et al 2011). Versiani et al (Versiani et al 2011)
12 beschrijft dat de 4 vergelijkende retrospectieve studie geen verschil aantonen in
13 klinische uitkomst tussen ECT en antidepressiva (Black et al 1987, Perris and
14 d'Elia 1966, Avery and Winokur 1977, Homan et al 1982). In de studies die ECT
15 response vergelijken tussen patiënten met een unipolaire en bipolaire depressie
16 lijkt de effectiviteit zeer vergelijkbaar (Loo et al 2011, Versiani et al 2011). Alle
17 5 prospectieve studies die ECT bij unipolaire en bipolaire depressie vergelijken is
18 ECT even effectief op klinische uitkomst maten (Daly et al 2001, Grunhaus et al
19 2002, Sienaert et al 2009, Stromgren 1973, Medda et al 2009), in 2 studies
20 hadden bipolaire patiënten minder ECT sessies nodig (Daly et al 2001, Sienaert
21 2009). Een recente meta analyse vond dat 50.9% (n = 402 / 790) van de
22 unipolaire patiënten herstelden na ECT behandeling en 53.2% (n = 168 / 316)
23 van de bipolaire patiënten (Dierckx et al 2012).

24 Veel onderzoeken zijn gedaan in therapieresistente patiënten met een bipolaire
25 depressie, als er voor deze patiënten gezocht wordt naar een behandeloptie van
26 hoogst mogelijk wetenschappelijk bewijs is ECT een goede behandeloptie
27 (Sienaert et al 2013).

28 Onderhoudsbehandeling

29 Onderhoudsbehandeling met ECT kan terugval in depressie voorkomen, dit is
30 vooral onderzocht bij unipolaire depressies, maar sommige naturalistische
31 studies hebben ook patiënten met een bipolaire depressie geïncludeerd (Vaidya
32 et al 2003). Onderhoudsbehandeling met ECT kan overwogen worden bij
33 bipolaire patiënten na een ECT behandeling voor depressie, manie of gemengde
34 episode en bij patiënten die eerder zijn teruggevallen onder farmacotherapie
35 (Loo et al 2011).

36 Patiënten met een beloop waarbij de episodes elkaar snel opvolgen dat er niet of
37 nauwelijks nog sprake is van een tussen liggend herstel (rapid cycling) kunnen
38 ook verbeteren met een onderhoudsbehandeling met ECT (Minnai et al 2011).

39