Development of a decision tool for early identification of adult patients with severe and complex bipolar disorder psychopathology in need of highly specialized care

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Abstract

Bipolar disorder is a complex and severe mental disorder. Despite evidence-based pharmacological and psychosocial interventions, complete stability is only reached by a small proportion of people who have BD, with over 90% of BD patients relapsing into new mood episodes during their lifetime. However, tools to differentiate patients who benefit sufficiently from standardized guideline treatment from patients who need more intensive or highly specialized treatment are lacking. The aim of the current study is to develop a decision tool for bipolar disorder that aids clinicians in early identification of a complex disease course in patients with bipolar disorder that are in need of highly specialized tertiary treatment. An earlier literature review led to the identification of 37 factors associated with a more unfavorable and complex disease course. Based on two expert rounds, using the Delphi method seven items were selected for the final tool: insufficient symptomatic recovery, comorbid personality problems, rapid cycling pattern, trauma, somatic comorbidity, psychiatric comorbidity, (the wish to become) pregnant. The pilot validation study indicated that the tool demonstrated good validity to identify patients for highly specialized tertiary care. A total score of ≥3 was found to represent an optimal cut-off point for identifying bipolar patients in need of highly specialized care. The currently developed decision tool could aid clinicians in identifying complex and severe pathology in bipolar disorder in early stages of diagnoses and treatment and subsequently allocating patients to highly specialized treatment. Validation in larger samples sizes is needed to make this tool generalizable to healthcare systems where early identification of severe cases is needed, across and beyond the Netherlands.

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1. Introduction

Bipolar disorder (BD) is a recurrent chronic mental disorder characterized by fluctuations in mood state and energy (Grande, Berk, Birmaher, & Vieta, 2016). It affects 1-2% of the world's population, irrespective of nationality, ethnicity, or socioeconomic status. The onset of the disorder is often around early adulthood and patients experience significant life adversity and disability in all functional domains of their lives (Nitzburg et al., 2016). The mood symptoms associated with BD are disruptive and lead to death by suicide in approximately 15% of patients (Thompson et al., 2003). In younger age groups, this risk is even higher, which is why BD is considered to perhaps be the most lethal of all psychiatric disorders (Berk et al., 2007). Patients have more suicide attempts and rate their life quality as poorer compared to those suffering from other mental disorders (Ten Have, Vollebergh, Bijl, & Nolen, 2002). Even though BD is considered one of the most genetically mediated mental disorders, the role of environment is often underestimated. The concordance rates of BD in identical twins is estimated to be 50%-60%, and only 50% of patients with BD have a positive family history in first-degree relatives, leaving considerable room for environmental influences (Post & Leverich, 2006).

A distinction can be made between type I and type II BD, whereby type II patients experience a weaker form of mania which lasts for shorter periods of time, called hypomania. The ratio of depression to mania in bipolar I is 3:1, whereas in bipolar II the ratio of depression to hypomania is 47:1, which makes a misdiagnosis of unipolar depression especially frequent at the onset of the latter (Berk et al., 2007). 75% of type I patients are also psychotic during their manic episodes. Different specifiers, like mixed episodes and rapid cycling, indicate that BD is a complex disorder which is difficult to be put into context (Grande et al., 2016). Comorbidity with other mental disorders is very high. 92% of patients seem to have at least one other diagnosis, of which 70% had a lifetime prevalence of at least three other psychiatric disorders, and between 20% and 60% of BD patients seem to have one or more personality disorders (Merikangas et al., 2007). BD typically has an onset in adolescence, but there is a significant delay of treatment, particularly in young people (Roy-Byrne, Post, Uhde, Porcu, & Davis, 1985): the average treatment delay amounts up to 9 years (Baethge et al., 2003). This certainly is one of the factors that contribute to a poorer overall functioning, through for instance increased unemployment rates and poorer relationships.

Management of the disorder results in substantial societal costs. One study estimates that in the US alone, treatment of all depression-related disorders amounts to 43 billion US Dollars a year, while the vast majority of affected people receive false diagnoses and inappropriate treatment or no treatment at all (Hirschfeld et al., 1997). Another study estimated the more broad direct and indirect national societal costs of BD alone to be 151

billion US Dollars in 2009 (Dilsaver, 2011). Even though mania is the defining pole of BD, depression is the dominant pole, leading to more adverse outcomes (Gitlin & Miklowitz, 2017) and having an especially strong and consistent effect on decreased productivity in the workplace (Simon, Ludman, Unützer, Operskalski, & Bauer, 2008). In one study, 60% of patients were unable to return to their occupational or educational role 1 year after being hospitalized for an acute episode (Loftus & Jaeger, 2006).

These outcomes could be substantially improved with appropriate therapy. There even is evidence that appropriate therapy is more beneficial to bipolar patients compared to patients with other disorders (Post & Leverich, 2006). Positive response to treatment unequivocally decreases as the disorder develops and becomes more chronic, which again highlights the importance of early intervention (Berk et al., 2010). However, such intervention is made substantially more difficult by the sheer amount and diversity of the aforementioned complicating factors. For example, the heterogeneity within the group of BD patients, with many different somatic and psychiatric comorbidities, makes it hard to find the right treatment and impossible to come up with a universal form or intensity of treatment. Moreover, the lack of research about effective treatment methods, or about tailoring different treatment methods to the respective appropriate patient subgroups, is reflected in the treatment guidelines, which show a lack of detail and room for improvement (see for example NICE, 2014).

1.1 Bipolar Disorder in the Netherlands

The lifetime prevalence of BD in the Netherlands is 1.9% (Ten Have et al., 2002). Almost three quarters of these patients do not receive appropriate treatment. In the Netherlands, treatments of mental disorders are generally carried out within the GGZ (geestelijke gezondheidszorg). The GGZ system is divided into three stages: (1) Basic care for milder pathology, often consisting of short-term psychotherapy; (2) specialized care for more complex or severe pathology; (3) highly specialized care for the most severe or complex cases (Netwerk Kwaliteitsontwikkeling GGz, 2017).

In the Netherlands, BD is treated within the specialized or highly specialized setting. Patients with especially severe and complex psychopathology usually have a history of unsuccessful treatment in specialized care before they enter highly specialized care. Several multidisciplinary teams with specific expertise about BD function as providers of this more intensive care. They are responsible for both the diagnostic process and treatment of BD. Only stabilized patients can be referred back to specialized care or to the general practitioner. The treatment of BD is based on national (Kupka et al, 2015) and international (NICE, 2014) guidelines and the Dutch care standard bipolar disorders (Netwerk Kwaliteitsontwikkeling GGz, 2017). The care standard is based on knowledge gained from scientific research, clinical experience and the preferences of patients and their relatives.

The treatment is arranged in several stages (Kupka & Knoppert-van der Klein, 2008): First is the acute treatment phase, usually lasting a few weeks, where the focus lies on decreasing the severity of the symptoms. The second phase is the continuing treatment, which

normally takes between 6 and 12 months and has a higher focus on self-management, where medication is resumed and possibly adjusted and psychoeducation for the patient as well as his or her relatives is offered. In addition, skills for relapse prevention are taught (for example with the help of a life chart or social rhythm matrix) and assisted reintegration into society is carried out. After continuing treatment, it is decided whether the patient requires preventive maintenance treatment, taking several years. This often the case for patients who already had several episodes. Regular treatment consists of medication, somatic controls, psychoeducation, social-psychiatric support and promoting self-management. Additional psychotic symptoms are treated with antipsychotic medication and by creating a structured and safe environment for the patient (Netwerk Kwaliteitsontwikkeling GGz, 2017).

Despite these carefully assembled treatment modalities, there is a high risk of relapse: In one study (Gitlin, Swendsen, Heller, & Hammen, 1995) investigating a sample of 82 BD outpatients, 73% relapsed into mania or depression after five years, 37% within one year. Even intensive pharmacological maintenance treatment did not prevent a relatively poor outcome for most patients. This makes it extra important for the patients to understand that they are suffering from a long-term, relapsing condition that needs self-management and engagement with care professionals.

It also makes an effective distinction between “regular” patients and those with more complex and severe forms of the disorder desirable - ideally before this manifests in a poor treatment response: Instead of the current referral to highly specialized care only if specialized care proves insufficient, patients with more severe difficulties could be helped more quickly and efficiently, instead of going through a lengthy and frustrating process to find the help that they need.

1.2 Psychotherapy in Bipolar Disorder

Psychotherapy could be applied additionally after the acute phase. It can be directed at the disorder itself, at comorbid conditions, or at the process of personal recovery. The efficacy of psychotherapy has only been studied in combination with patients also receiving medication, and it is likely that treatments without any medication are insufficient, especially in BD I. It is not clear which form of psychological therapy is most effective in which phase of treatment (Kupka et al., 2015), but it is uncontroversial that psychotherapy is helpful for patients with BD: A recent meta-analysis (Oud et al., 2016) of 55 randomized controlled trials showed that psychological interventions are effective in reducing relapse rates, hospital admissions and symptom severity at post-treatment and follow-up. The effects were mild to moderate. Individualized treatment is recommended by the authors, so it seems clear that a one-fits-all approach is, as for most mental disorders, unsuitable and that treatment has to be personalized and adjusted to each individual patient.

Nevertheless, care standards do not specifically address which patient characteristics require which treatment options and thus also which patients can be considered to require highly specialized care. This leads to problems at both sides: mental health professionals have

to repeat work that has already been done at the earlier stage, while patients have to follow a frustrating and exhausting path of trial and error before finding the right treatment. Moreover, one also has to attend to the fact that the mental healthcare system has a budget constraint, which is why not all patients can be provided with extensive treatment that includes psychotherapy and other more thorough approaches only implemented at the highly specialized stage. Therefore, it is urgently necessary to be able to quickly and reliably identify those patients who, on the one hand "suffer the most", i.e. have the most complex and severe form of the disorder, and on the other hand are most likely to benefit from additional, more intensive, multidisciplinary treatment. A recently designed, fairly easy and effective way to do both of these things is with the help of a decision tool.

1.3 Decision tool

Even though it is a difficult task to operationalize them (Dingemans et al., 2017), clearly defined factors associated with the severity of the disorder and the degree of psychosocial functioning of the patients are needed to be able to help with tailoring treatment at an early stage. Recently developed decision tools make use of such factors and thereby allow clinicians to make a distinction between patients who are confronted with problems making them eligible for standard specialized care and patients with serious, more complex, problems who are eligible for highly specialized care in the Dutch mental healthcare system. Thus, they are meant to separate the patients who require more intensive treatment from those who do not. It is expected that direct referral to highly specialized care, instead of a stepped care approach, is more beneficial to these patients. The goal of such a decision tool can be summarized as preventing ineffective treatment for the patients.

There exists a transdiagnostic decision tool in the Netherlands (van Krugten et al., 2020), but in practice its threshold is inappropriately low, because due to the already inherent severe and complex nature of bipolar disorder almost all BD patients would meet criteria for highly specialized care using this tool. There also by now exist decision tools for depression (van Krugten et al., 2019), eating disorders (Dingemans et al., 2017), anxiety disorders (not published yet), and personality disorders (Goorden et al., 2017). Up until now, there have been no efforts to develop a decision tool specifically for Bipolar Disorder. In light of the importance and urgency of that task, this will be the aim of the present study.

The aim of the present study is to carry out an empirically sound development (step 1) and preliminary validation (step 2) of a new decision tool, by examining which psychological factors are most useful in identifying complexity and severity of the disorder and comparing the compiled factors to the clinical judgment of clinicians.

2. Method

2.1 Design & Procedure

2.1.1 Literature Review. As a first step, a literature review was carried out to identify criteria indicating a more complex and severe course of the disorder. These are important to consider while planning the further treatment of patients. For example, a history of trauma predisposes people not only for a higher risk of developing BD, but also for a more severe course (Netwerk Kwaliteitsontwikkeling GGz, 2017). This work was done as part of another Master Thesis project. Out of this review resulted 37 criteria, some of which were eventually to be included as items on the newly developed decision tool. A list of all the criteria can be found in Appendix A.

The criteria identified in the literature review were then discussed among a focus group of experts who all work in specialized outpatients clinics for bipolar disorders. A special emphasis was laid on the clinical significance and applicability of the identified factors. Several factors that were deemed relevant by the experts, but which had not been found during the literature review process, were consequently added to the list.

2.1.2 Delphi Method. For the data collection phase, the Delphi Method was used (Dalkey, 1969). It has the aim of measuring the level of agreement between raters and reaching a consensus (Graham, Regehr & Wright, 2003). It enables anonymity between participants with controlled and structured feedback, because there are several rounds of data collection. In the first round, group members respond independently to statements. In the rounds thereafter, they are presented with the average ratings from all group members and asked to reflect on and potentially adjust their earlier rating. It is a method where no direct discussion takes place and therefore any consensus can only derive from the information provided by the researchers as opposed to other group processes, like group think or peer pressure, whereby some group members could hold back their opinion to fit in (Janis, 2008). Two rounds of data collection were used. In both rounds, consensus was to be achieved on the importance of the above-mentioned factors. The respondents were asked to submit their answers within a two-week period. After one week, a reminder was sent to them.

2.1.3 Expert Round 1. In the first round, items that were potentially useful for the decision tool were evaluated. They were presented to a panel of experts in the treatment of BD, who had not been previously involved in the usage or development of decision tools. An online questionnaire was created and sent to these experts. Each of the 37 items was presented with the instruction to indicate its relevance in predicting the complexity and severity of the disorder and the necessity for highly specialized care. The experts were asked to rate the relevance of each item on a 5-point likert scale (1 – completely irrelevant, 5 – extremely relevant). An item was considered relevant if the score given was >= 4. In addition, they were asked to indicate if they found that any important items were missing on the list, if they had

comments about the existing items (for example, if any overlapped so considerably that they could be combined into a single item) and if they had any additional comments or questions. If less than 60% of experts rated an item as relevant (score 4 or 5), it was not included in the second round. Before the second round, feedback from the first round was used for modification of several items (see results).

2.1.4 Expert Round 2. Another questionnaire including the items with the highest ratings from the first round was sent to the same experts. In this second Delphi round, the average score from the first round was presented with each item. The experts were again asked to evaluate the relevance of the presented items (1-5). Consensus was achieved when more than 70% of the experts considered an item as relevant. This is a common cut-off score which has been used in similar mental health research using a single expert panel (Jorm, 2015; Dingemans et al., 2017; Hidalgo-Mazzei et al., 2019). After this round, feedback was again discussed and small adjustments were made on items.

2.1.5 Validation round. As a third step, the decision tool tested in clinical practice to determine its inter-rater reliability (do different clinicians use the tool in a similar enough way when presented with the same patients?), criterion validity (do the items on the decision tool properly reflect what is clinically significant in referring patients to highly specialized care?) , and cut-off score (how many items on the decision tool have to be present for a patient so that he/she qualifies for highly specialized care?).

This was done in two steps: First, the expert panel wrote case descriptions of five actual patients they recently saw in their clinical practice, who all met several items on the decision tool. All patient data were properly anonymized so that the actual individuals were not recognizable. A third online questionnaire was sent to the same clinicians who participated in expert rounds 1 and 2. They received the instruction to rate the cases on the decision tool. The resulting data was used to calculate the inter-rater reliability.

Second, the decision tool was tested among a small subset of patients during the intake phase within three different treatment facilities. For each patient, two clinicians made their usual clinical decision regarding highly specialized care (yes/no) and subsequently filled in the decision tool. Their clinical judgment forms the reference standard for the analysis of the criterion validity of the decision tool, since there are no other psychometric measures to compare it against and this judgment of experienced professionals is deemed a valid directive.

2.2 Participants

For rounds one and round two, the raters were recruited via a convenience sample of 28 experts from highly specialized care clinics in Rotterdam, Utrecht and Deventer. These were 9 men and 19 women, their mean age was 45.6 (sd=10.1, range=28;71), and their mean years of experience was 10.7 (sd=10, range=1;49). Their professions were (clinical)

psychologists, psychiatrists, and (specialized) nurses. Table 1 shows the demographic characteristics and professions of participants.

Table 1: *Demographics of participants*

Factor	N (%)
Gender	
Total	28 (100)
Male	9 (32)
Female	19 (68)
Years of Experience	
Total	28 (100)
Less than 5 years	5 (18)
5-10 years	10 (36)
11-15 years	4 (14)

More than 15 years	4 (14)
Unknown	5 (18)
Profession	
Total	28 (100)
(Clinical) Psychologist	7 (25)
Psychiatrist	9 (32)
(Specialized) Nurse	12 (43)

2.3 Statistical analysis

All analyses were conducted using SPSS (Statistical Package for the Social Sciences) version 20.0 (IBM SPSS version 20, New York, NY, USA). Characteristics of the raters were examined using descriptive statistics. Inter-rater reliability of the third validation round was assessed by Krippendorff's alpha (Hayes & Krippendorff, 2007). A binomial logistic regression was performed to calculate the probability of each item on the decision tool to predict a 'highly specialized care' decision. The dependent variable was the clinical judgment (tertiary care yes/no) and the independent variables were each of the seven factors on the decision tool (present/not present). Linearity of the dataset was ascertained before carrying out the analysis. The Nagelkerke R square value (equivalent of R^2 in multiple regression analysis) was calculated to show how much variation in the dependent variable can be explained by the regression model. Sensitivity and specificity were calculated using the classification table. Statistical significance of each independent variable were calculated with the equation table. The difference on scored/present items for patients referred to highly specialized and standard care, respectively, was calculated using an independent samples t test.

3. Results

3.1 Expert rounds 1&2

In the first round, consensus was achieved on 19 of the initial 37 criteria. Some of these were then combined during another focus group discussion were the feedback of experts from the first round was considered and inconsistencies were identified. The two items "Comorbid somatic illness that could interfere with treatment" and "Comorbid somatic problems caused by treatment" were combined into one item ("Somatic comorbidity or somatic problems caused by medication that could interfere with treatment"). In addition, items indicating comorbidity with a specific psychiatric disorder (autism, ADHD, eating disorder, and anxiety disorders respectively) were all combined into one overarching "comorbid psychiatric disorder" item. The item "Limited insight into or acceptance of the disorder" was extended to "Limited insight or acceptance and/or limited opportunities to learn

or follow instructions". Finally, "emotion regulation problems" were included under "personality problems". This led to a total of 16 items rated in the second round.

Table 2 shows the 16 highest-ranking items from round one and their different ratings from both rounds (% of participants that gave 4-5 points per round, average score per round, total score per round). Overall, the ratings given after re-assessment in round two were lower than those in round one. The first 9 items were chosen to be included in the decision tool, since their overall consensus in round two was above 70%. These are insufficient symptomatic recovery, Treatment-resistant depression, trauma, psychiatric comorbidity, rapid cycling, somatic comorbidity, (wish to become) pregnant, personality problems, and dysfunctional coping. Appendix A shows all 37 items that were found in the literature review.

Another focus discussion, which had the aim of comparing the results of the questionnaires with the common manifestations of bipolar pathology in clinical practice, concluded that it would be clearer to include the item 'treatment-resistant depression' under 'insufficient symptomatic recovery' and to include 'dysfunctional coping' under 'personality problems'. Thus, 7 criteria remained: Insufficient symptomatic recovery, trauma, psychiatric comorbidity, rapid cycling, somatic comorbidity, (wish to become) pregnant, and personality problems.

This led to the final selection of seven items for the decision tool: (1) insufficient symptomatic recovery (e.g. treatment-resistant depression); (2) comorbid personality problems and/or dysfunctional coping, including but not limited to one or more diagnosed personality disorders; (3) a rapid cycling pattern (≥4 mood episodes per year); (4) serious and/or prolonged trauma during childhood or later in life; (5) somatic comorbidity, which might also be caused by current psychopharmacological treatment (e.g. lithium); (6) psychiatric comorbidity (e.g. anxiety disorder, ADHD, autism, substance abuse); (7) patient is pregnant or has the wish to become pregnant.

Table 2: *Results of round 1 and 2*

Item		% Participants that gave 4-5 round 2	Average score round 2	Total score round 2 (n=26)	% Participants that gave 4-5 round 1	Average score round 1	Total score round 1 (n=28)
1.	Insufficient symptomatic recovery	92	4,38	114	93	4,43	124
2.	Treatment-resistant depression	85	4,19	109	93	4,39	123

3.	Trauma	85	4,00	104	79	4,04	114
4.	Psychiatric comorbidity	81	4,00	100	-	3,60	-
5.	Rapid Cycling	77	4,00	104	86	4,25	119
6.	Somatic comorbidity	77	3,80	99	82	4,16	117
7.	(Wish to become) pregnant	73	3,92	102	86	4,21	118
8.	Personality problems	73	3,88	101	82	4,07	116
9.	Dysfunctional coping	73	3,88	101	68	3,89	109
10.	Interpersonal problems	69	3,77	98	75	3,89	110
11.	Nonadherence to medication	69	3,88	101	68	3,89	109
12.	Lack of insight/acceptance	62	3,65	95	68	3,89	109
13.	Substance abuse	58	3,73	97	79	3,93	113
14.	Other psychosocial problems	50	3,48	87	68	3,75	108
15.	Mixed Episodes	42	3,34	87	64	3,86	109
16.	Depression with psychosis	42	3,31	86	71	3,75	108

3.2 Interrater reliability

The Krippendorff's alpha test was used (Hayes & Krippendorff, 2007) to estimate the inter-rater reliability based on the rating of 5 clinical cases in the validation round. The results show that the inter-rater reliability was relatively high: $\alpha = 0.694$. This means that the 14 raters did show an acceptable agreement on the presence or absence of items from the decision tool for the five presented cases.

3.3 Validation round

In this round, the decision tool was tested in clinical practice to determine its criterion validity and a preliminary cut-off point. The number of cases referred to highly specialized care by the clinicians was 22 out of 62 (35%). All other 40 cases were referred to standard

care. The mean number of items scored positively for a highly specialized care decision was 3.45. Therefore, the preliminary cut-off score was set at 3 out of 7 items. The mean number of items scored positively for a standard care decision was, by comparison, 1.5. Figure 1 shows the frequency of items rated as present per decision (standard/highly specialized care). Table 4 shows the frequency of individual items on the decision tool as rated by the clinicians.

Table 4: *Frequency of individual items on the decision tool as rated by clinicians*

		Frequency	**Percent**
Insufficient symptomatic recovery	Yes	23	37.1
	No	39	62.9
	Total	62	100
Rapid Cycling	Yes	6	9.7
	No	56	90.3
	Total	62	100
Somatic comorbidity	Yes	19	30.6
	No	43	69.4
	Total	62	100
Trauma	Yes	24	38.7
	No	38	61.3
	Total	62	100
Personality problems	Yes	35	56.5
	No	27	43.5
	Total	62	100
Psychiatric comorbidity	Yes	27	43.5
	No	35	56.5
	Total	62	100
(wish to become) pregnant	Yes	5	8.1
	No	57	91.9
	Total	62	100

An independent samples t-test showed that the 40 patients referred to highly specialized care (M = 1,5, SD = 1.04) compared to the 22 patients referred to standard care (M = 3,45, SD = 1.06) demonstrated significantly lower scores on the decision tool, t (60) = 7.01, p = <.01, with a mean difference of 1.95 (95% CI 2.97; 0.94).

A binomial logistic regression was performed to calculate the probability of each item on the decision tool to predict a 'highly specialized care' decision. The dependent variable was the clinical judgment (tertiary care yes/no) and the independent variables were each of the seven factors on the decision tool (present/not present). Table 5 shows the results of the regression analysis.

Linearity of the data was ascertained. The model explained 83.8% (Nagelkerke R^2) of the variance in clinical judgment and correctly classified 90.3% of cases. Sensitivity (percentage of cases referred to highly specialized care which were correctly predicted by the model, 'true positives') was 81.8% and specificity (percentage of cases not referred to highly specialized care which were correctly predicted by the model, 'true negatives') was 92.5%.

Table 5: *Results of the binomial logistic regression*

Variable	**B**	**S.E.**	**Wald**	**Exp ß**	**df**	**Sig. (p Value)**
Insufficient recovery	-3.795	1.470	6.664	.022	1	.010
Rapid cycling	-24.594	15759.255	.000	.000	1	.999
Somatic comorbidity	-3.052	1.325	5.309	.047	1	.021
Trauma	-.569	1.032	.305	.566	1	.581
Personality problems	3.160	1.555	4.129	.042	1	.042
Psychiatric comorbidity	.127	1.190	.011	1.136	1	.915
(wish to become) pregnant	-.415	.977	.181	.660	1	.671

The items that significantly predicted whether, according to the clinicians, patients were in need of highly specialized treatment were 'insufficient recovery' (p = .010), 'somatic comorbidity (p = .021) and 'personality problems' (p = .042). The other items did not appear to be significant.

4. Discussion

The aim of this study was to develop a decision tool for better recognition of patients with a severe course of bipolar disorder that will enable clinicians to refer them more efficiently to highly specialized (tertiary) treatment programs. For the final tool, seven items are suggested based on a systematic review and different expert rounds according to the Delphi method. These are (1) insufficient symptomatic recovery, including treatment-resistant depression; (2) comorbid personality problems and/or dysfunctional coping, including but not limited to one or more diagnosed personality disorders; (3) a rapid cycling pattern; (4) serious and/or prolonged trauma during childhood or later in life; (5) somatic comorbidity, which might also be caused by pharmacological treatment (e.g. lithium); (6) psychiatric comorbidity (e.g. anxiety disorder, ADHD, autism); (7) patient is pregnant or has the wish to become pregnant.

The decision tool shows adequate inter-rater reliability and a total score of ≥3 was found to represent an optimal cut-off point for identifying bipolar patients in need of highly specialized care. Patients who by clinical judgment were indicated to need highly specialized care scored significantly higher on items of the decision tool than patients who were indicated to need standard care. Insufficient recovery, somatic comorbidity and personality problems were shown to be able to significantly predict clinicians' decision in referring patients to highly specialized care. This is only a first evaluation of the tool´s validity, since in clinical practice it will not be single items on the decision tool that have a decisive effect, but a combination of several. Future research could investigate which combinations of items signify a marked need for highly specialized care.

Psychiatric comorbidity cannot significantly predict a referral to highly specialized care, because this item already applies to most patients. The literature suggests that 92% of BD patients are diagnosable with one or several comorbid disorders (Merikangas et al., 2007). It not clear if the clinicians understood correctly what exactly was meant to be included under 'psychiatric comorbidity', since many disagreements on this factor for the same patient were found. Therefore, we suggest to always provide an additional instruction sheet with explanations about to the decision tool in future research. It should also be noted that the decision tool is meant to be filled in quickly by the clinician during an intake, so the criteria will in practice be based more on broad clinical impression than on careful diagnostic testing.

One strength of the study is that we recruited patients and questioned experts from three different treatment facilities known for professional highly specialized treatment, thereby leading to a broad generalizability. Moreover, the questioned experts were highly experienced, with an average of 10 years. Another strength is the use of several rounds that all made use of evidence-based strategies of data collection, thus combining the latest insights from scientific research with actual clinical knowledge and bridging the gap between theory and its application in practice. Furthermore, the anonymous nature of the Delphi method allowed for no face-to-face contact, which reduces the proneness to faulty judgment processes like individuals bending to the will of the group. The criteria were beforehand gathered in a literature review and experts were able to add additional criteria during the first round, which made the process of achieving consensus more rigorous and open.

The are also several limitations: one is that the decision tool does not (yet) give practitioners the opportunity to weigh single items more heavily than others if deemed necessary, or to rate a specific combination of items as more important than others. This was also mentioned in the feedback provided by the experts. The tool is also based on criteria that overlap and among which establishing clear boundaries is not possible. For example, it might be that a patient suffers from multiple diagnosable personality disorders and severe early-childhood trauma, which leads to excessive self-harming behavior. Even though only 2 of the 3 items that are necessary for highly specialized treatment ('comorbid personality problems' and 'trauma') are applicable in this case, the practitioner decides that this specific combination weighs more heavily than others and directly refers the patient to tertiary care. In such cases it is advisable for professionals to put their clinical experience before a decision reached only by filling in the tool. Relevant weightings and combinations could be addressed in future discussions among experts, which could result in a short manual that would enable the clinicians to use the decision tool more efficiently. Another limitation is that cut-off points for the individual criteria were not (yet) established. Therefore, two different clinicians might have different notions about what exactly 'dysfunctional coping' consists of or how many 'psychiatric comorbidities' qualify as sufficient.

Timely recognition and adequate treatment of BD can have great consequences for the quality of life of patients. The same can be said about identifying the most complex and severe cases. With this decision tool, care providers could be able to offer more tailored treatment to the individuals who need it most. They could also be able to carry out earlier and more precise recognition of who these individuals are. This will, in the long run, hopefully lead to a more goal-oriented and differentiated treatment of bipolar disorder. It should be noted that determining a tailored treatment for patients with a disorder as complex as BD remains a difficult and multi-faceted decision, which should always be carried out by well-trained practitioners. A decision tool should be viewed as an addition to clarify this challenging process instead of a surrogate to simplify it.

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Appendix A: Factors as used in the first questionnaire

1. Bipolar II diagnosis
2. Rapid cycling pattern
3. Mixed episodes
4. Emotion regulation problems
5. Treatment-resistant depression
6. Comorbid anxiety disorder
7. Comorbid eating disorder
8. Comorbid ADHD
9. Comorbid autism spectrum disorder
10. Comorbid somatic illness that could interfere with treatment
11. Comorbid somatic problems caused by treatment (for example, kidney problems caused by prolonged lithium use)
12. History shows manic episode with psychotic features
13. History shows depressive episodes with psychotic features
14. Early-childhood trauma or trauma later in life
15. Dysfunctional coping strategies (for example, avoidant, externalizing, or ruminating)
16. Limited insight into or acceptance of the disorder
17. Personality problems (includes a diagnosed personality disorder)
18. Delay of treatment between 6 and 10 years
19. Delay of treatment more than 10 years
20. Patient is younger than 25
21. Patient is older than 60
22. History shows an attempted suicide
23. Incomplete recovery in spite of previous specialistic treatment in line with treatment guidelines
24. Predominant polarity of depression
25. Functional cognitive limitations (for example, memory or attention problems)
26. Mild alcohol consumption (more than one unit per day more than once per week)
27. Alcohol or substance abuse
28. Hopelessness independent from depressive symptomatology
29. A BMI higher than 30 (obesity)

30. Patient is a woman with a child wish or pregnancy
31. Patient is a man who will become father soon
32. Patient is a woman in menopause
33. Nonadherence to medication or the wish to stop with medication
34. Systemic problems (for example, high EE within family) or lack of social support
35. Other psychosocial problems that could influence the treatment or course of the disorder
36. Patient has problems with existential questions (for example, finding meaning within his or her life)
37. Patient is cognitively less able

Appendix B: Factors as used in the first questionnaire (Dutch)

1. De gestelde diagnose is een bipolaire II stoornis
2. Er is sprake van een rapid-cycling patroon
3. Er is sprake van gemengde stemmingsepisodes
4. Er is sprake van emotie-regulatie problematiek
5. Er is sprake van een therapieresistente depressie
6. Er is sprake van een comorbide angststoornis
7. Er is sprake van een comorbide eetstoornis
8. Er is sprake van comorbide ADHD
9. Er is sprake van een comorbide autisme spectrum stoornis
10. Er is sprake van een co-morbide somatische aandoening die kan interfereren met de behandeling
11. Er is sprake van somatische problemen veroorzaakt door de behandeling (bijvoorbeeld, nierfunctie achteruitgang bij langdurig lithium gebruik)
12. Er is in de voorgeschiedenis sprake van een manische episode MET psychotische kenmerken
13. Er is in de voorgeschiedenis sprake van een depressieve episode MET psychotische kenmerken
14. Er is sprake van vroegkinderlijk trauma of trauma later in het leven
15. Er is sprake van disfunctionele coping strategieën (bijvoorbeeld, vermijden, externaliseren of piekeren)
16. Er is sprake van beperkt ziekte inzicht en/of acceptatie
17. Er is sprake van persoonlijkheidsproblematiek
18. Patiënt heeft voorafgaand aan de behandeling tussen de 6 en 10 jaar klachten gehad waarvoor geen behandeling is geweest
19. Patiënt heeft voorafgaand aan de behandeling meer dan 10 jaar klachten gehad waarvoor geen behandeling is geweest
20. Patiënt is jonger dan 25 jaar

21. Patiënt is ouder dan 60 jaar
22. Er is sprake geweest van een suïcidepoging in het verleden
23. Er is sprake van onvoldoende herstel ondanks specialistische behandeling conform de richtlijn
24. Er is sprake van onvoldoende herstel ondanks specialistische behandeling conform de richtlijn
25. Het beloop wordt gekenmerkt door overwegend depressieve episodes
26. Er is sprake van functionele cognitieve beperkingen (bijvoorbeeld geheugen- of aandachtsproblemen)
27. Er is sprake van milde alcoholconsumptie (meer dan 1 keer in de week meer dan 1 eenheid per dag)
28. Er is sprake van alcohol- of middelenmisbruik
29. Er is sprake van hopeloosheid los van depressieve symptomatologie
30. Het BMI is hoger dan 30 (obesitas)
31. Patiënte betreft een vrouw met een kinderwens/zwangerschap
32. Patiënt betreft een man die binnenkort vader wordt
33. Patiënte betreft een vrouw in de menopauze
34. Er is sprake van medicatie-ontrouw of de wens om met de medicatie te stoppen
35. Er is sprake van systeemproblematiek (bijvoorbeeld, hoge EE binnen familie) of gebrek aan sociale steun
36. Patiënt ervaart zingevingsproblematiek en/of existentiële levensvraagstukken
37. Er is sprake van zwakbegaafdheid

Appendix B: The decision tool as used in the clinical validation round

Decision Tool Bipolair TOP GGZ – klinische validatieronde

Gegevens mbt de intake:
Instelling:

- □ **Altrecht**
- □ **Dimence**
- □ **Ingeest**

Datum van de intake (dd/mm/jj):
Leeftijd van de patiënt:
Laatste letter van de achternaam vd patiënt:

Oordeel clinicus alvorens invullen decision tool:
Voor welke zorg-zwaarte indiceert u deze patiënt op basis van uw klinische oordeel?

- □ **Specialistische GGZ**
- □ **TOP klinische GGZ**

Criterium	Aankruisen
1. Is er sprake van onvoldoende symptomatisch herstel (o.a. therapieresistente depressie)?	□ Ja □ Nee

2. Is er sprake van een rapid cycling patroon?	□ Ja □ Nee
3. Is er sprake van somatische comorbiditeit (al dan niet als gevolg van de behandeling)?	□ Ja □ Nee
4. Is er sprake van ernstige en/of langdurige traumatisering in de kindertijd of later in het leven?	□ Ja □ Nee
5. Is er sprake van een comorbide persoonlijkheidsproblematiek en/of disadaptieve coping, die interfereert met de behandeling (bijv. vermijding, externaliseren)?	□ Ja □ Nee
6. Is er sprake van andere comorbide psychiatrische problematiek (bijv. angst, ADHD, autisme, aan middel gebonden stoornis)?	□ Ja □ Nee
7. Is er sprake van een kinderwens/ zwangerschap?	□ Ja □ Nee

Appendix C: Case descriptions as used in the validation round online questionnaire

Casus 1

Een 48-jarige man, alleenstaand, arbeidsongeschikt verklaard vanwege zijn bipolaire I stoornis. Is sinds 4 jaar in behandeling op een specialistische polikliniek, echter op 21 jarige leeftijd gediagnosticeerd met de bipolaire stoornis. Gebruikt lithium en er zijn meerdere medicamenten geprobeerd tegen zijn terugkerende depressies (oa lamotrigine, antidepressiva) zonder succes. Ook andere interventies zoals zelfmanagement groep, IPSRT en CGT hebben geen effect gehad. Ondanks behandeling maakt patiënt jaarlijks een hypomane/manische episode door van zo'n 2-3 weken, daarop volgt een depressie die aanhoudt tot de volgende manie. Er is geen sprake van tussentijds herstel.

Hij heeft een zeer beperkt steunsysteem dat bestaat uit 1 vriend en zijn ouders die al op hoge leeftijd zijn. Er is sprake van familiaire belasting met psychische aandoeningen. Moeder heeft in de kindertijd van patiënt ernstige recidiverende depressies gehad met psychotische kenmerken. Toen hij 7 was deed zij een ernstige TS (eigen keel doorgesneden) waarna zij 3 jaar in een psychiatrische inrichting heeft gezeten.

Somatische is er sprake van overgewicht (BMI 34) en patiënt lijdt aan slaapapneu.

Patiënt is behandeltrouw, maar lijdt erg onder zijn depressies. Hij zou graag vrijwilligerswerk doen, maar dit houdt hij niet vol vanwege zijn aanhoudende instabiliteit.

Casus 2

Een 26-jarige vrouw met een bipolaire I stoornis. Patiënte is aan het promoveren. Heeft op haar 24ste de eerste manische episode doorgemaakt. Reageert goed op lithium mono-therapie en is sindsdien stabiel. Vindt het moeilijk om open te zijn naar haar omgeving over de bipolaire stoornis, vooral in de context van haar werk. Zij stelt zeer hoge eisen aan zichzelf en wil niet als zwak gezien worden. Zij heeft daarom ook moeite met aanpassingen die zij moet doen om stabiel te blijven (grenzen bewaken, op tijd op de rem). Momenteel liggen haar ouders in scheiding en is er sprake van een conflict tussen moeder en patiënte. Dit geeft haar stress. Patiënte zelf heeft een stabiele relatie en een goed steunsysteem. Zij is somatisch gezond. Patiënte gaat binnenkort trouwen met haar huidige partner. Daarna wil zij proberen zwanger te worden.

Casus 3
Een 34 jarige man, getrouwd met 2 kinderen, werkzaam bij een verzekeringsmaatschappij lijdt aan een bipolaire II stoornis. De hypomane episodes zijn goed onder controle met lithium, echter patiënt ervaart wel terugkerende depressieve episodes. Deze lijken vooral samen te hangen met piekerklachten. Patiënt heeft bij een licht dalende stemming sterk de neiging te gaan piekeren, dusdanig dat hij ernstige slaapproblemen ontwikkelt waardoor zijn stemming verder daalt. De piekerklachten voldoen aan de DSM 5 criteria van een gegeneraliseerde angststoornis. Patiënt heeft een steunende partner die betrokken is bij de behandeling. Door de terugkerende klachten is patiënt enkele keren uitgevallen op werk, hij is zelf bang zijn baan te verliezen door zijn veelvuldige verzuim. Hij heeft het daar erg naar zijn zin. Daarbij heeft patiënt 2 jaar terug een hernia gehad, en ervaart hij tijdens depressieve episodes terugkerende rugklachten. Patiënt is ambivalent ten opzichte van de medicatie, omdat hij nog wel de depressieve episodes ervaart, maar niet zijn productieve en energieke hypomane episodes. Hij mist deze kant van zichzelf.

Casus 4
Een 49-jarige vrouw getrouwde vrouw met 2 volwassen kinderen, met een bipolaire I stoornis. Sinds 15 jaar is er sprake van recidiverende depressies waarvoor sinds 10 jaar nortriptyline nadat bij instelling op venlafaxine een hypomanie optrad, tevens gebruikte patiënte in depressieve episoden tijdelijk antipsychotica (zuclopentixol, olanzapine) vanwege angst, agitatie en . Drie jaar geleden werd zij opgenomen vanwege een eerste manisch-psychotisch toestandsbeeld. Sindsdien is patiënte ingesteld op valproïnezuur en fluanxol naast de nortriptyline. Sinds de opname is er een rapid cycling patroon waarin perioden waarin het heel goed gaat, mogelijk hypomane episodes, gevolgd worden door langdurige depressieve episodes. Onderhoudend in de depressieve episodes is het ontbreken van een daginvulling sinds de kinderen zelfstandig zijn geworden. Patiënte maakt een stressgevoelige indruk, een vakantie in het vooruitzicht of een verjaardag zorgt voor overmatig piekeren en sombere gevoelens. Er is sprake van EPS en beginnende tardieve dyskinesie bij langdurig antipsychoticagebruik. Sinds 4 jaar is patiënte bekend met epilepsie en zij wordt behandeld voor hypertensie en hypercholesterolemie

Casus 5
Een 29-jarige man, alleenstaand na een relatie van 10 jaar die een half jaar eerder verbroken is, patiënt werkt als evenementen planner. Patiënt is door de crisisdienst verwezen nadat hij een tentamen suïcide heeft gedaan met lachgas, benzodiazepinen en een zak over het hoofd.

Patiënt heeft uiteindelijk zelf hulp ingeschakeld. De crisisdienst beschrijft een persisterende doodswens en tevens een behandelwens. In het verleden is patiënt bij gediagnosticeerd met ADHD en een bipolaire stoornis. Tevens is er sprake van overmatig middelen gebruik (alcohol, ketamine, XTC, cocaïne, ritalin, LSD, DMT). Patiënt gebruikt methylfenidaat maar zonder voorschrift van een arts. Tijdens intake werd een patiënt gezien die herhaaldelijk benoemt een laagzelfbeeld en zelfhaat te hebben. De manische episoden bestaan uit het hebben van verhoogde energie te, het sturen van onprettige berichten en een andere logica hebben. De depressieve episoden bestaan uit het hebben van weinig energie, geen interesse hebben, niet van de bank komen en geen eetlust hebben. Tijdens depressieve perioden is er sprake van automutilatie.