Journal of Affective Disorders 170 (2015) 166–171

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

The prevalence and effect of life events in 222 bipolar I and II patients: A prospective, naturalistic 4 year follow-up study

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ARTICLE INFO

Article history:
Received 25 April 2014
Received in revised form
29 July 2014
Accepted 7 August 2014
Available online 6 September 2014

Keywords:
Bipolar disorder
Life event
Stress
Mood disorders
Relapse

ABSTRACT

Background: Life events may very well increase the likelihood of affective episodes in bipolar disorder, but prospective data on survival are inconsistent.
Methods: The authors examined the prevalence of negative and goal-attainment life events within 6 months prior to the index episode and after the index episode and their impact on the risk of relapse. Two hundred twenty-two consecutively admitted ICD-10 bipolar I ($n=126$) and II ($n=96$) patients were followed-up naturalistically over a period of 4 years.
Results: One-hundred thirty-eight (62.2%) of the patients had at least one life event 6 month *before* the index episode. Seventy patients (31.5%) experienced one, 48 (21.6%) two, and 20 (9.0%) three (or more) life events. Regarding life events *after* the index episode, 110 (49.5%) patients had at least one life event. Fifty-four patients (24.3%) experienced one, 31 (14.0%) two, and 25 (11.3%) three (or more) life events. The number of life events was larger in patients with bipolar II disorder than in patients with bipolar I disorder ($p=0.004$). Using a Cox regression analysis, the risk of a depressive relapse in bipolar I patients was associated with the number of life events after the index episode ($p=0.002$). This was independent of the quality of the life event.
Limitations: Standardized life event scales, defined dosages of drugs or blood sampling during all visits were not performed.
Conclusions: Our data suggest a high and continuous number of life events prior to affective episodes. Life events after the index episode worsened the course of bipolar I patients with more depressive episodes. This underlines the importance of detection and treatment of emerging life events.

1. Introduction

Bipolar disorder is a severe chronic disorder and is the sixth leading cause of disability among physical and psychological disorders worldwide (Murray and Lopez, 1996). Despite advances in the treatment of bipolar disorder, almost 70% of 300 bipolar I and II patients relapse within 4 years, with a mean of 208 days until the next affective episode (Simhandl et al., 2014). This pattern highlights the need to better understand the predictors of illness course, including psychosocial factors, which received an increasing awareness lately. Considerable literature exists about the prevalence of life events prior to episodes and its role on the course of bipolar disorder (Ambelas, 1979; Christensen et al., 2003; Dunner et al., 1979; El Kissi et al., 2013; Ellicott et al., 1990; Garno et al., 2005; Gershon et al., 2013; Hosang et al., 2012; Hosang et al., 2010b; Joffe et al., 1989; Kennedy et al., 1983; Neria et al., 2005; Swendsen et al., 1995). Stressful life events are associated with lower socio-economic status, living with non-intact family, anxiety and disruptive behaviors (Romero et al., 2009) and occur frequently prior to affective episodes in bipolar patients (Ambelas, 1979; Dunner et al., 1979; El Kissi et al., 2013; Hosang et al., 2010a). As a clinical consequence bipolar patients with prior life events take three times as along to achieve recovery as those without (Johnson and Miller, 1997). However, data are contradictive in terms of the effect of life events on relapses: Some retrospective (Joffe et al., 1989; Kennedy et al., 1983) and prospective studies (Christensen et al., 2003; Ellicott et al., 1990; Swendsen et al., 1995) proposed a negative impact on the course of bipolar patients, especially on depressive episodes (Gershon et al., 2013), whereas other prospective studies did not reveal such a correlation (Johnson et al., 2008; McPherson et al., 1993; Pardoen et al., 1996). All above mentioned studies have important methodological limitations such as small sample sizes, limited observational

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http://dx.doi.org/10.1016/j.jad.2014.08.043
0165-0327/

periods (1–2 years) or the inclusion of bipolar I patients only. Therefore, we aimed to clarify the role of life events in bipolar disorder in a large prospective study with a long observational period, including both bipolar I and II patients. By evaluating life events both *before* and *after* the index episode, we studied the delayed and acute effects of life events on the course of the illness separately. The acute effects were assessed by analyzing the influence of life events *after* the index episode, i.e. immediately before the relapse. The delayed effects were evaluated analyzing the influence of the life events *before* the index episode, i.e. a longer time before the relapse, and by evaluating an episode and its remission between both the event and the relapse.

2. Methods

2.1. Study design

The trial was a prospective, naturalistic, observational study, conducted in the County Hospital Neunkirchen, Austria, from 2000 through 2008 (Simhandl et al., 2014). All diagnoses were made following ICD-10 criteria based on a detailed clinical interview and review of case-notes carried out by two independent psychiatrists. For additional psychiatric co-morbidities the Mini-International Neuropsychiatric Interview (MINI) was used which is validated for DSM-IV and ICD-10 (Sheehan et al., 1998). At admission, demographical and clinical variables were collected for the entire sample, including physical co-morbidities. Exclusion criteria were limited to the presence of neurological diseases. During their admissions all patients were informed about their diagnoses, possible risk factors and the importance of pharmacological treatment.

Bipolar patients entered the prospective follow-up in either a hypomanic/manic index episode, in a depressive index episode with or without psychotic symptoms or with “other syndromes” as index episode. “Other syndromes” were defined as anxiety disorder, mixed episode, or rapid-cycling following ICD-10 criteria. After discharge, patients typically remitted clinically and were treated by their own psychiatrist. They subsequently were evaluated in person at least once a year in the outpatient clinic of the hospital (78%), via telephone contact or personal contact with their own psychiatrist (22%). No affective rating scales were applied. At follow-up visits, the psychiatrists in charge of the study entered their evaluation in a specially developed web-based database with regard to affective relapses, adherence to treatment, and occurrence of life events, amongst others. Relapses were defined as a deterioration or change of the affective state needing an explicit pharmacological intervention and/or re-hospitalization. In case of a severe mood episode patients continued the study and received additional follow-up. Patients who died a natural death or who committed suicide were dropped from the study. All data were always directly entered into the self-developed web-based database.

The study was approved by the ethical committee of the University of Vienna, Austria, and all patients provided written informed consent for participation in a long-term clinical study. The trial has been registered as www.clinicaltrials.gov with registration number: NCT01792128.

2.2. Subjects

In total, 515 bipolar I and II patients were consecutively admitted to the local psychiatric hospital in Neunkirchen, Austria, from 2000 through 2004. Of 515 admitted patients 366 (71.1%) agreed to participate and signed the informed consent at discharge. Of those, 66 (18%) patients did not enter the follow-up period after discharge from the hospital due to the following reasons: one patient (0.3%) moved to another country, 23 (6.3%) received a different diagnosis when they were re-diagnosed and 31 (8.4%) could not be contacted. Furthermore, 5 (1.4%) died from a natural death and 6 (1.6%) from suicide. Seventy-eight other patients had to be discarded from this study because data on life events after the index episode could not be adequately collected. Thus the final analysis included data from 222 bipolar I ($n=126$) and II ($n=96$) patients during 4 year-follow-up, with at least two evaluation data.

All patients were prescribed typically used drugs in bipolar disorder, in mono-therapy or in combination. Treatment was not influenced by the study protocol and included lithium, valproate, carbamazepine, lamotrigine or atypical antipsychotics, such as olanzapine, risperidone or quetiapine. Additionally, patients were also treated with antidepressants (mainly SSRIs), benzodiazepines, and medication for physical co-morbidities (mainly for hypertension, diabetes and thyroid dysfunction).

2.3. Life events

Life events were evaluated *before* and *after* the index episode using the standardized interview and were directly entered in the web-based database. Negative life events were defined as loss of employment, loss/change of residence, end of sentimental relationship, loss of a confidant or family member, accident with admission to hospital, admission to a psychiatric hospital, personal crisis, court case, violence, or all these events experienced by a related person (classified as “others”). Goal-attainment life events were defined as new relationship, marriage, pregnancy/birth and new job/change of employment. Life events could be multiple but given that only 5 patients had four life events before the index episode, and only 1 patient had four life events after the index episode, these were added to the group with three life events.

2.4. Database

The web-based database was especially designed for this study with the objective of an uncomplicated data entry via internet. All participating psychiatrists ($n=9$) were instructed in the use of the database and personally entered corresponding data of their patients, thus avoiding errors that often occur during transcription of medical record to study protocol, and eventually data entry into the database. The principal investigator of the study, CS, and the statistician, BK, regularly checked the correctness of entered data.

2.5. Statistics

Relationships between the number of life events and demographic and clinical variables were assessed using linear regressions for continuous variables (age) and binary logistic regressions for binary variables (sex, disorder type and adherence to medication). Relationship between the number of life events and the time to relapse was assessed using Cox proportional hazards regression models. These analyses were also separately conducted for manic and depressive relapses and for patients with bipolar I and bipolar II disorder.

All analyses were conducted with the base and ‘survival’ (Therneau and Lumley, 2011) package for R (http://cran.r-project.org/).

3. Results

3.1. Demographical and clinical data

All relevant demographical and clinical baseline data are highlighted in Table 1.

Table 1
Demographic and clinical baseline data of 222 bipolar I and II patients.

	All	Bipolar I ($n=126$)	Bipolar II ($n=96$)
Sex	Women: 155 (69.8%) Men: 67 (30.2%)	Women: 93 (73.8%) Men: 33 (26.2%)	Women: 62 (64.6%) Men: 34 (35.4%)
Age (at index episode, years)	44.7 (SD=13.1)	44.3 (SD=13.0)	45.4 (SD=13.1)
Marital status[a]	Married: 119 (53.8%) Not married: 102 (46.2%)	Married: 72 (57.1%) Not married: 54 (42.9%)	Married: 47 (49.5%) Not married: 48 (50.5%)
Family history of psychiatric disorders[b]	Yes: 110 (53.1%)	Yes: 61 (53.0%)	Yes: 49 (53.3%)
Comorbidities[d]	Physical: 145 (67.1%) Psychiatric: 102 (45.9%)	Physical: 78 (62.9%) Psychiatric: 40 (31.7%)	Physical: 67 (72.8%) Psychiatric: 62 (64.6%)
Age at onset of the disease (years)	32.4 (SD=12.0)	31.1 (SD=11.6)	34.2 (SD=12.3)
Episodes before index episode[c]	Mean: 5.5 episodes None: 9 (4.3%) 1 episode: 40 (19.2%) 2–3 episodes: 53 (25.5%) 4–6 episode: 58 (27.9%) 7 or more: 48 (23.1%)	Mean: 5.4 episodes None: 4 (3.4%) 1 episode: 21 (17.8%) 2–3 episodes: 28 (23.7%) 4–6 episode: 38 (32.2%) 7 or more: 27 (22.9%)	Mean: 5.7 episodes None: 5 (5.6%) 1 episode: 19 (21.1%) 2–3 episodes: 25 (27.8%) 4–6 episode: 20 (22.2%) 7 or more: 21 (23.3%)
Admissions before index episode	Mean: 2.2 admissions None: 81 (36.5%) 1 admission: 49 (22.1%) 2–3 admissions: 50 (22.5%) 4 or more: 42 (18.9%)	Mean: 2.3 admissions None: 47 (37.3%) 1 admission: 27 (21.4%) 2–3 admissions: 27 (21.4%) 4 or more: 25 (19.9%)	Mean: 1.9 admissions None: 34 (35.4%) 1 admission: 22 (22.9%) 2–3 admissions: 23 (24.0%) 4 or more: 17 (17.7%)
Index episode (at study entry)[e]	(Hypo) Mania: 46 (21.1%) Depression: 131 (60.1%) Other[(f)]: 41 (18.8%)	(Hypo) Mania: 43 (34.4%) Depression: 49 (39.2%) Other[(f)]: 33 (26.4%)	Hypomania: 3 (3.2%) Depression: 82 (88.2%) Other[(f)]: 8 (8.6%)
Number of life events *before* the index episode	Mean: 1.0 life events None: 84 (37.9%) 1 event: 70 (31.5%) 2 or more: 68 (30.6%)	Mean: 0.9 life events None: 52 (41.3%) 1 event: 41 (32.5%) 2 or more: 33 (26.2%)	Mean: 1.2 life events None: 32 (33.3%) 1 event: 29 (30.2%) 2 or more: 35 (36.5%)
Number of life events *after* the index episode	Mean: 0.9 life events None: 112 (50.5%) 1 event: 54 (24.3%) 2 or more: 56 (25.2%)	Mean: 0.7 life events None: 70 (55.6%) 1 event: 32 (25.4%) 2 or more: 24 (19.0%)	Mean: 1.1 life events None: 42 (43.8%) 1 event: 22 (22.9%) 2 or more: 32 (33.3%)
Adherence to medication	Good: 80 (36.0%) Poor: 142 (64.0%)	Good: 56 (44.4%) Poor: 70 (55.6%)	Good: 24 (25.0%) Poor: 72 (75.0%)

[a]1 data missing.
[b]15 data missing.
[c]14 data missing.
[d]6 data missing for physical comorbidities.
[e]4 data missing.
[f]Other: anxiety disorders, mixed episodes and rapid cycling (following ICD-10 criteria).

3.2. Prevalence of life events before and after the index episode

One-hundred thirty-eight (62.2%) of the patients had at least one life event 6 months *before* the index episode. Seventy patients (31.5%) experienced one, 48 (21.6%) two, and 20 (9.0%) three (or more) life events. Regarding life events *after* the index episode, 110 (49.5%) patients had at least one life event. Fifty-four patients (24.3%) experienced one, 31 (14.0%) two, and 25 (11.3%) three (or more) life events. There was a weak positive correlation between the number of life events before the index episode and the number of life events after the index episode ($r=0.260$, $p<0.001$).

3.3. Relationship between demographical data and life events

The number of life events was larger in bipolar II than in bipolar I patients ($p=0.004$). This relationship was separately observed for life events *before* and *after* the index episode, though it was not significant after correction for multiple comparisons in the former ($p=0.049$ and 0.009, respectively). The number of life events was also larger in patients with a bad adherence to medication ($p=0.029$), though again this relationship was not significant after correction for multiple comparisons and it could be detected only for life events *before* (but not *after*) the index episode ($p=0.006$ and 0.433, respectively). No relationships were noted between the number of life events and the age or sex of the patients.

3.4. Course of the illness depending on presence of life events before and after the index episode

There were no relationships between the number of life events *before* the index episode and the risk of relapse. Conversely, the risk of a depressive relapse was associated with the number of life events *after* the index episode, though only in patients with bipolar I disorder (Table 2 and Fig. 1). The risk of a manic relapse was not associated with the number of life events after the index episode. No association of life events *before* or *after* the index episode with depressive episodes in bipolar II disorder was deteceted.

Hypomanic episodes could not be associated with life events. This was due to the design of the original study protocol which did not consider hypomanic phases as relapses as they are often dificult to diagnose and patients frequently do not consult their psychiatrist to discuss hypomanic symptoms (see definition of relapses in the study design). Therefore, only depressive but not hypomanic episodes could be calculated in this way in the bipolar II sample.

3.5. Quantitative comparison of negative life events and goal-attainment life events

We also compared the effect of negative life events and goal-attainment life events on the course of the illness separately. We found a statistically significant increased risk of a depressive relapse for goal-attainment life events after the index episode in bipolar I disorder ($p=0.010$), and an increased risk of a depressive relapse for negative life events after the index episode in all patients ($p=0.009$).

4. Discussion

To the best of our knowledge, this is the largest and longest prospective study investigating the prevalence and role of life events prior to affective relapses in bipolar I and II disorder. We found evidence that 138 (62.2%) of 222 bipolar patients experienced at least one life event 6 months prior to the index episode and 110 (49.5%) after the index episode. This suggests a rather stable and high prevalence of life events prior to affective relapses during the course of the illness. Our finding is in line with data by Hosnang and colleagues who reported that bipolar patients frequently experienced at least one negative life event 6 months prior to their worst depressive episode (63.7%) and manic episode (62.8%) when compared to controls (48.4%) 6 months prior to the interview (Hosang et al., 2010a). Further studies revealed a high prevalence of negative life events prior to affective episodes, ranging from about 50% ($n=79$; (Dunner et al., 1979)) to 88% ($n=60$; (El Kissi et al., 2013)).

We also found a weak positive correlation between the number of life events before the index episode and the number of life events after the index episode. This may imply that suffering from current life events increases the risk of life events in the future, in the sense that past life events "cause" new life events. Alternatively, it is also possible that underlying factors, such as co-morbid personality disorders, continuously increase the risk of life events.

Interestingly, we found strong evidence that the number of life events was larger in bipolar II than in bipolar I patients. However, we could not detect a negative effect of life events on depressive episodes in bipolar II patients. This is noteworthy as bipolar II patients probably suffer from more affective relapses than bipolar I patients, as suggested by a recent meta-analysis of relapse rates of naturalistic bipolar studies (Amann and Radua, 2014). Unfortunately and as stated before, we cannot draw conclusions on the effect of life events on hypomanic episodes in our bipolar II sample as hypomanic episodes were not defined as relapses in the original study protocol. In general, evidence of consequences of life events on bipolar II patients is scarce as three prior prospective, naturalistic studies included bipolar I patients only (Gershon et al., 2013; Johnson et al., 2008; McPherson et al., 1993) and two studies included only 13 bipolar II patients (Swendsen et al., 1995) and 11 bipolar II (Pardoen et al., 1996). One further study ($n=56$) did not specify the bipolar type (Christensen et al., 2003). Adding up the evidence we obtained so far, no conclusion can be drawn with respect to hypomanic episodes but – at least in our study – no effect of life events has been observed in depressive episodes in bipolar II disorder.

A central finding of our study is that life events play an important role in bipolar I disorder as they clearly worsened the course of the disease by triggering more depressive episodes. The fact that only those life events occurring shortly before the relapse (i.e. after the index episode) cause an effect on affective episodes, may indicate that life events have an acute (rather than a delayed) effect on the risk of relapse and/or that life events per se and not other underlying factors (e.g. co-morbid personality disorder) are triggers for more affective relapses. Some earlier prospective studies, with smaller sample sizes and shorter observational periods, proposed also a negative impact on the course of bipolar patients in case of acute life events prior to the index episode (Christensen et al., 2003; Ellicott et al., 1990; Swendsen et al., 1995).

Table 2
Effects of the number of life events *after* the index episode on the Risk of Manic and Depressive Relapse.

	Hazard ratio (per life event)	95% CI	*z*	*P*
All patients ($N=222$)				
All relapses ($n=154$)	1.15	0.99–1.33	1.84	0.0655
Only manic relapses ($n=34$)	0.80	0.56–1.16	−1.16	0.246
Only depressive relapses ($n=98$)	1.33	1.12–1.58	3.22	0.001[a]
Bipolar-I patients ($N=126$)				
All relapses ($n=78$)	1.29	1.03–1.62	2.24	0.025
Only manic relapses ($n=30$)	0.86	0.55–1.34	−0.65	0.513
Only depressive relapses ($n=34$)	1.64	1.20–2.25	3.08	0.002[a]
Bipolar-II patients ($N=96$)				
All relapses ($n=76$)	0.96	0.79–1.16	−0.45	0.655
Only depressive relapses ($n=64$)	1.02	0.83–1.26	0.20	0.841

N: number of patients; *n*=number of relapses.
[a]Significant after Bonferroni-correction for multiple comparisons.

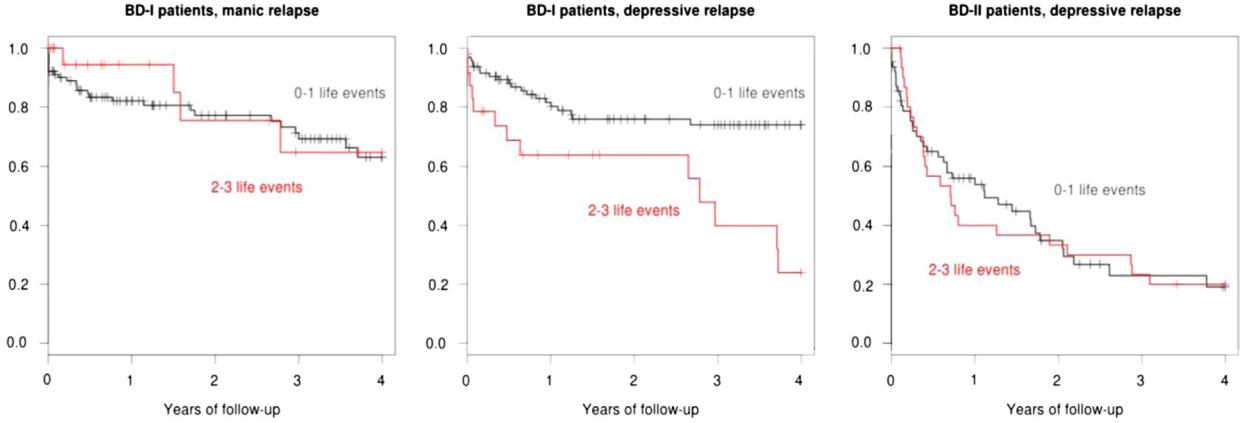

Fig. 1. Effects of the Number of Life Events *after* the Index Episode (i.e. shortly before the relapse) on the Risk of Manic and Depressive Relapse. *Legend to* Fig. 1: Kaplan Meyer plots showing the percentage of patients that had not relapsed after a given time of follow-up, shown separately for patients with none or one life event after the index episode (black line) and patients with two or more life events after the index episode (red line).(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A recent prospective study by Gershon et al. (2013) investigated the influence of chronic stressors and trauma in 130 bipolar I patients over the course of two years. Interestingly and supportive for our data, severity of the stressors predicted depressive but not manic symptoms. Another cross-sectional study supports the effect of life events on the depressive pole of the disease: the authors suggested a significant interaction between the Met containing BDNF Val66 Met genotype and stressful life events, such as serious illness, injury, death of a close person, separation, serious conflict or job loss, for the worst depressive but not manic episodes (Hosang et al., 2010b). This is a gene-environmental relevant finding as the "neurotrophic hypothesis" suggests a stress induced reduction of BDNF activity which triggers decreased hippocampal functioning and depressive episodes (Stein et al., 2008).

In contrast, no effect of life events was found in our study on manic episodes in bipolar I disorder. This challenges data which stem from the effect of both positive and negative life events on bipolar disorder (Johnson et al., 2008). This study suggested more manic symptoms as consequence of goal-attainment life events, such as acceptance into graduate school, making partner in a law firm, getting married, being hired for a job, amongst others. In our study we evaluated some positive life events, such as new job, new relationship, marriage, and pregnancy/birth as goal-attainment life events but did not find any specific effect on manic relapses. As stated above, another study found also an association of negative life events with manic episodes (Hosang et al., 2012), a finding which was not replicated in our study.

However, our findings underline the importance of detection but especially of treatment of life events in bipolar disorder. So far, treatment options in this population are scarce. However, a recent randomized controlled trial found beneficial effects of Eye Movement Desensitization Reprocessing Therapy on mood and trauma symptoms in sub-syndromal bipolar patients with a history of traumatic life events (Novo et al., 2014).

4.1. Limitations

Methodological caveats of our study must be taken into account when translating results to clinical work. Firstly, it has to be noted that we evaluated typical negative and goal attainment life-events but did not use standardized life event scales, such as the interview of recent life events by Paykel (Paykel, 1997), the List of Threatening Experiences Questionnaire (Brugha et al., 1985) or for goal attainment events (Leenstra et al., 1995). Furthermore, we did not evaluate either severe trauma, or severe childhood trauma. Various studies suggest an important impact of severe trauma or PTSD as co-morbidity on the onset and course of the illness (Cutajar et al., 2010a, 2010b; Dell'osso et al., 2014; Garno et al., 2005; Goldberg and Garno, 2005; Leverich et al., 2002; Neria et al., 2005; Shonkoff and Garner, 2012). Therefore, no conclusions can be drawn if they were prevalent and if so, whether they exerted an influence on the course of the disease. Both issues might have influenced presented results.

Obviously, some strict methodological issues of RCTs could not be integrated in the design of a naturalistic, observational study, such as defined dosages of drugs or blood sampling during all visits. Conversely, we obtained results of a long observation period from a large sample of "real world" bipolar I and II patients with psychiatric and physical co-morbidities.

5. Conclusions

Our study confirms evidence of a high prevalence of life events before and after the index affective episodes; the latter being associated to more depressive episodes in bipolar I disorder. This finding underlines the importance of a continuous detection and treatment of life events in bipolar patients.

Role of funding source

Development of the web-based interview and database was funded by the Österreichische Forschungsförderungsgesellschaft mbH (FFG) which is the Austrian Federal Department for Transport, Innovation, and Technology, Department of Innovations and Telecommunications. Additional support came from the Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) and by the Instituto de Salud Carlos III, Spain, with a Miguel Servet Research Contract (CP06/0359) and Research Projects (PI07/1278 and PI10/02622) to Benedikt L Amann.

Conflict of interest

The authors do not have any conflicts of interest related to this manuscript.

Acknowledgments

We acknowledge support by the Research Group Industrial Software Engineering of the Technical University of Vienna and their department head Prof. DI Dr. Thomas Grechenig. Furthermore, we thank Drs. Jutta Bilonoha, Elisabeth Denk, Birgit Gasselseder, Jens Mersch, Klaudia Mitterwachauer, Stephanie Schiebel, Christian Wunsch, Ali Zoghlami and Daniela Renhofer for data entry. The authors acknowledge support from Thomas Simhandl BSc, for the first version of the web-based interview and data base. We also thank Marylou Salou for editing and revising the manuscript.

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