Age at Onset of Bipolar Disorder Related to Parental and Grandparental Illness Burden

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ABSTRACT

Objective: The age at onset of bipolar disorder varies greatly in different countries and continents. The association between load of family history of psychiatric illness and age at onset has not been adequately explored.

Methods: 979 outpatients with bipolar disorder (from 4 sites in the United States and 3 in the Netherlands and Germany) gave informed consent and completed a questionnaire about their demographics, age at onset of illness, and family history of unipolar and bipolar disorder, alcohol and substance abuse comorbidity, suicide attempts, and "other" illnesses in their parents, 4 grandparents, and any offspring. We examined how the parental and grandparental burden of these illnesses related to the age at onset of the patients' bipolar disorder.

Results: The burden of family psychiatric history was strongly related to an earlier age at onset of illness in both US and European patients ($F_{3,906} = 35.42$, $P < .0001$). However, compared to the Europeans, patients in the United States had both more family history of most difficulties and notably earlier age at onset. Earlier age at onset was associated with a greater illness burden in the patient's offspring ($t_{568} = 4.1$, $P < .0001$).

Conclusions: More parental and grandparental psychiatric illness was associated with an earlier age at onset of bipolar disorder, which is earlier in the United States compared with Europe and is strongly related to a poor long-term prognosis. This apparent polygenic contribution to early onset deserves further study and therapeutic attempts at ameliorating the transgenerational impact.

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While there has been some controversy about the role of diagnostic thresholds in the increases in the number of office visits for childhood-onset bipolar illness in the United States in recent years, other factors could include lack of previous recognition, real increases based on cohort and anticipation effects, and accompanying more severe illness necessitating more office visits. Whatever the fundamental explanations turn out to be, data from a variety of sources suggest that there is a higher incidence of childhood onset bipolar disorder in the United States compared to many European countries and perhaps even Canada. The higher incidence in the United States is evident in clinical samples,[1–5] epidemiologic studies that include the consideration of bipolar disorder not otherwise specified in the data,[6,7] and a wealth of retrospective data from adults.[8–12] These studies suggest that two-thirds of adults with bipolar disorder in the United States experienced onset of illness prior to age 19 years, while only one-third had an onset prior to age 19 in the Netherlands and Germany. Thirty-one percent experienced onset of illness before age 13 in the United States compared with only 5% in Europe.[13] Convergent with these findings are the ages at onset of children at high risk because of a parent with bipolar disorder that were conducted in the United States versus other countries. Studies in the United States of children at risk because of a family history of bipolar disorder[1,2,14–19] show a very substantial incidence of childhood onset bipolar disorder compared to negligible amounts in European or Canadian studies.[18,20–22]

The reasons for this disparity in age at onset across different countries are unclear. Part of the explanation for the low age at onset of bipolar disorder in the United States appears to be the higher incidence of 2 of the major risk factors for early onset—genetic and psychosocial stress vulnerability.[10,13,23]

The current study was undertaken to further explore the association of early age at onset with (1) the burden of multiple psychiatric illnesses in family members and (2) assessments of grandparents as well as parents. We postulated that a greater burden in the family of multiple psychiatric problems (including bipolar and unipolar mood disorders; anxiety, alcohol, and substance abuse comorbidity; "other" psychiatric illness; and history of a suicide attempt) would be associated with an earlier

Clinical Points

- Parental and grandparental diverse psychiatric illnesses other than bipolar disorder are rarely considered as risk factors for childhood-onset bipolar disorder.
- Early onset of bipolar disorder is related to the total family history of illness burden, with a diagnosis of depression or "other illnesses" conveying independent risk, and illnesses in the patient's mother are especially important.
- Compared to those with adult-onset illness, parents with early-onset bipolar disorder have children with more psychiatric illness; this offspring illness burden is greater in the United States than in Europe and deserves increased clinical, research, and public health attention.

age at onset of bipolar disorder. We further hypothesized that these familial influences on early-onset bipolar disorder would show some nonspecificity, in that different types of illnesses beyond bipolar disorder in the parents and grandparents would influence the early age at onset of bipolar disorder in our patients.

The experience of abuse and other stressors in childhood has also been associated with an early age at onset of bipolar illness, quite likely based on lasting environmentally induced epigenetic effects.[24] We hypothesized that the occurrence of these childhood adversities would also contribute to an early age at onset of bipolar disorder.

METHODS

Outpatients (mean age = 40 years) with bipolar disorder (75% bipolar I) diagnosed by Structured Clinical Interview for *DSM-IV* Disorders (SCID)[25] were recruited from advertisements and local clinics in 4 cities in the United States (Los Angeles, California; Dallas, Texas; Cincinnati, Ohio; and Bethesda, Maryland) and 3 in Europe (Utrecht, the Netherlands, and Freiburg and Munich, Germany). The network was funded by the Stanley Foundation from 1995 to 2002, and patients were recruited and studied during this period. The Stanley Foundation played no role in the analysis or the interpretation of these data. Patients gave informed consent for participation in the network under the National Institute of Mental Health institutional review board (IRB)–approved protocol and separately under the IRB at each academic institution at each site. Patients completed self-rated questionnaires on demographics, family history, and their retrospective course of illness.[9,10,23,26–28]

In the family history section of the questionnaire, each parental diagnosis was rated by the proband as definite, probable, possible, or not present, and a definite or probable rating was taken as a positive diagnosis for that parent.[10,23] The diagnoses rated included unipolar depression, bipolar disorder, history of a serious suicide attempt or completed suicide, alcohol abuse, drug abuse, or "any other psychiatric illness" with the specific examples given as "(ie, anxiety, panic attacks, eating disorders, attention-deficit disorder, behavioral problems, obsessive-compulsive disorder, autism, etc)." The same ratings were also used for assessment of both maternal and paternal grandparents, any of the patients' siblings, and any of the patients' children.

The questionnaire also elicited answers pertaining to demographics, stressors in childhood, and course of illness characteristics, including the age at onset of bipolar disorder. This was described as the age at onset of the first major depression associated with dysfunction or the first manic or hypomanic episode. Stressors in childhood included a total score (maximum of 9 for a childhood adversity score) for the report of verbal, physical, and sexual abuse, each rated as (never, 0; rarely, 1; occasionally, 2; or frequently, 3) as previously described.[13,24] The mean age at network entry for the probands was 40.6 years in the United States and 40.3 in Europe; 57.9% were female in the United States, and 53.8% were female in Europe. The population was mostly white: 88.7% in the United States and 95.9% in Europe. As previously reported,[13] there were striking differences in the distributions of the ages at onset of the first episode of depression or mania. In the United States versus Europe, respectively, these onsets were in childhood (prior to age 13 years), 31.1% versus 5.6%; in adolescence (prior to age 19 years), 38.1% versus 28.6%; in young adulthood (prior to age 30 years), 19.8% versus 42.2%; and in late adulthood (30 years or older), 11.0% versus 23.7%.

The relationship between the total burden of family illness (ie, the sum of parental and grandparental illnesses together, or, separately, parental and grandparental illness) to age at onset in childhood (prior to age 13 years), adolescence (prior to age 19 years), early adulthood (prior to age 30 years), and late adulthood (31 years or older) was examined with a 1-way analysis of variance. This was examined both in our overall patient population and separately in the US and European populations. A series of multiple regressions then assessed whether the type of illness in the family, the total amount of all illnesses, or the family member who had the illness better predicted age at onset. The total childhood adversity score was assessed as an independent contributor to early age at onset using a regression analysis, controlling for country, gender, and age at network entry.

RESULTS

Table 1 shows the incidence rates of psychiatric illness in the probands' parents and grandparents. As illustrated in Table 2, there was a relationship between a family history of psychiatric illness and age of bipolar onset in the proband both in the overall population ($F_{3,906} = 35.42$, $P < .0001$) and separately in the US patients ($F_{3,621} = 14.03$, $P < .0001$) and the Europeans ($F_{3,281} = 4.42$, $P < .005$), such that patients whose direct relatives had a greater number of psychiatric problems had earlier ages at onset of bipolar disorder. Bonferroni post hoc tests for the overall population found that the 4 age at onset groupings (childhood, adolescence, early adulthood, and late adulthood) significantly differed from each other at at least the .001 level except for early adult versus late adult onset, which did not significantly differ in degree of family illness loading ($P = .314$).

Table 1. Percentage of Parents and Grandparents Positive for Each Type of Illness

	Alcohol Abuse	Bipolar Disorder	Unipolar Depression	Drug Abuse	Other	Suicide Attempt or Suicide
Maternal grandmother	5.8	9.6	19.6	2.8	9.1	3.1
Maternal grandfather	17.4	6.5	14.4	1.4	3.8	3.1
Paternal grandmother	4.9	7.8	19.2	1.3	6.8	2.0
Paternal grandfather	15.8	5.8	13.0	0.8	4.6	2.7
Any grandparent	28.7	22.1	37.9	5.0	15.5	9.0
Mother	9.4	16.7	31.9	5.9	21.5	9.3
Father	25.5	18.2	31.0	6.9	14.0	6.3
Any parent	29.3	29.6	48.7	10.7	27.7	13.7
Any parent or grandparent	42.6	36.3	58.2	13.6	31.3	19.5

Table 2. Increased Amount of Family Psychiatric Illness in Parents and Grandparents Associated With Earlier Age at Onset of Bipolar Disorder

	Age at Onset Grouping[a]					
Population	Child 0–12 y	Adolescent 13–18 y	Adult 19–29 y	Late Adult 30+ y	*F*	*P*
Overall	4.5 ± 0.3	3.3 ± 0.2	2.1 ± 0.2	1.4 ± 0.2	35.4	<.0001
United States	4.7 ± 0.3	3.8 ± 0.2	3.0 ± 0.3	2.0 ± 0.3	14	<.0001
Europe	1.9 ± 0.8	1.8 ± 0.2	1.3 ± 0.1	0.9 ± 0.2	4.4	.005

[a]Values expressed as mean ± SEM of the total number of illnesses that parents and grandparents of the bipolar patient had.

Figure 1. Greater Family Illness Burden Is Associated With an Earlier Age at Bipolar Onset

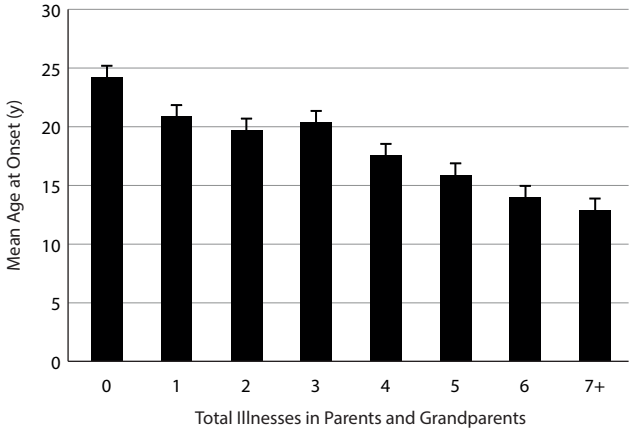

Figure 1 shows the dramatic relationship of total parental and grandparental illness to age at onset of bipolar disorder in the whole cohort. Those with no positive family history had a mean age at onset of 24.1 years, and this decreased rather linearly to a mean age at onset of 12.9 years in those patients with 7 or more cumulative illnesses in their parents and grandparents. A Pearson *r* found the negative correlation to be significant ($r = -0.33$, $n = 912$, $P < .001$). Similar significant relationships were observed in both the US and the European patients (data not shown). In those patients with no family history of psychiatric illness, the mean age at onset was still younger in those from the United States (22.3 years) compared to those from Europe (27.1 years).

We next examined how age at onset could be modeled by the family history of psychiatric illness findings. To do this, family illness was measured in 3 ways: the sum total of family illness in parents and grandparents; the types of illness that occurred in families; and the individual family member with illness. Each of the 3 family illness measures was run in a linear regression with gender, age at network entry, and country as controls. All 3 regressions produced models effective at predicting age at onset: sum of family illness, $F_{4,907} = 84.94$, $P < .0001$, adjusted $R^2 = 0.269$, root MSE 8.98; type of family illness, $F_{9,743} = 35.77$, $P < .0001$, adjusted $R^2 = 0.294$, root MSE 8.62; and family member who was ill, $F_{9,799} = 36.02$, $P < .0001$, adjusted $R^2 = 0.281$, root MSE 8.85. In each of the 3 analyses, an independent effect of country (United States earlier age at onset than the Netherlands and Germany) and of younger age of the patient at network entry were also significantly related to the patients' earlier age at onset.

The total family burden of psychiatric illness (in parents and grandparents) was related to earlier age at onset after controlling for country, age, and gender. The odds ratio was −0.68, standard error = 0.11, $z = -6.21$, $P < .001$, and 95% confidence interval, −0.90 to −0.47. To model the type of illness present in family members, the number of relatives with each illness category was calculated producing a score from 0 to 6 (2 parents and 4 grandparents). We found that both depression and "other psychiatric illness" in the 2 generations were inversely associated with the probands' age at onset (Table 3).

Table 3. Age at Onset as Predicted by the Sum of the Type of Illness in the Family Illness[a]

	Odds Ratio	SE	*z*	*P*	95% CI
Country	5.89	0.72	8.19	.00	4.48 to 7.30
Age at entry	0.34	0.03	12.06	.00	0.29 to 0.40
Gender	0.26	0.65	0.41	.68	−1.01 to 1.53
Depression	**−0.73**	**0.32**	**−2.27**	**.02**	**−1.37 to −0.10**
Bipolar	−0.39	0.42	−0.94	.35	−1.21 to 0.43
Alcohol	−0.10	0.39	−0.25	.81	−0.86 to 0.67
Drug	−0.67	0.71	−0.95	.34	−2.07 to 0.72
Suicide	−0.48	0.65	−0.73	.47	−1.76 to 0.81
Other	**−0.89**	**0.37**	**−2.42**	**.02**	**−1.62 to −0.17**

[a]Bold indicates a variable independently significant at .05 or less.

The influence of which family member was ill was measured by calculating the total number of illnesses in each family member, producing a score from 0 to 6. Total illness in the mother, but not other relatives, was significantly related to the probands' earlier age at onset (Table 4).

Table 4. Age at Onset as Predicted by Which Family Member Was Ill[a]

	Odds Ratio	SE	*z*	*P*	95% CI
Country	5.90	0.71	8.26	.00	4.50 to 7.30
Age at entry	0.32	0.03	11.87	.00	0.27 to 0.37
Gender	0.54	0.64	0.85	.40	−0.71 to 1.80
Mother	**−0.77**	**0.31**	**−2.44**	**.02**	**−1.38 to −0.15**
Paternal grandmother	−0.92	0.52	−1.78	.08	−1.94 to 0.09
Paternal grandfather	−0.68	0.49	−1.38	.17	−1.64 to 0.29
Father	−0.46	0.30	−1.52	.13	−1.06 to 0.13
Maternal grandfather	−0.15	0.49	−0.30	.76	−1.10 to 0.81
Maternal grandmother	−0.37	0.49	−0.77	.44	−1.33 to 0.58

[a]Bold indicates a variable independently significant at .05 or less.

The influences of childhood adversity and family history illness were examined in a multiple regression controlling for age, gender, and country ($F_{5,903} = 78.02$, $P < .0001$, adjusted $R^2 = 0.3$). Childhood abuse was considered any verbal, physical, or sexual abuse that occurred at least occasionally in childhood.[24,29] Abuse and family illness burden were both independently highly significant ($P < .001$) in relating to an earlier age at onset of bipolar disorder in the proband, although the strength of the overall regression remained very similar to that of just using total family illness alone. Thus, while there is some interrelationship between family history and stressors in childhood, each is an independent contributor and vulnerability factor for an earlier age at onset of bipolar disorder.

In a preliminary analysis, we also examined whether the amount of illness occurring in the patients' offspring was related to early- versus late-onset illness in the patient. An independent samples *t* test found that compared to patients with adult onsets of their bipolar disorder, those that had an early onset of their bipolar illness (prior to age 19) had offspring with a greater psychiatric burden ($t_{568} = 4.1$, $P < .0001$). The mean number of illnesses in the offspring of our patients with early onset was 0.81 versus 0.40 in those with late onset. Similarly, an independent samples *t* test showed that patients had an earlier age at onset of bipolar disorder (18.3 years) if their offspring had a psychiatric illness compared to a mean age at onset of 21.0 years in those who did not have offspring who were ill ($t_{570} = 2.69$, $P < .01$). We did not have age at onset data for the offspring to see if early-onset illness in the proband also bred true in the offspring.

DISCUSSION

As hypothesized, our data revealed a strong relationship of a range of parental and grandparental psychiatric difficulties to early age at onset of our adult outpatients with bipolar disorder. The highest total illness burden in both parents and grandparents was highly related to a markedly earlier average age at onset (12.9 years) compared to patients without a positive family history of any psychiatric illness (mean age at onset 24.1 years) reflecting a mean difference in age at onset of 11.2 years. Compared to those from Europe, patients from the United States had both an earlier age at onset of their bipolar disorder[9–12] and a much higher incidence of a positive history of multiple psychiatric difficulties in their parents and grandparents as seen here. Patients were also asked if any of these same illnesses that were assessed in parents and grandparent had appeared in any of their offspring. Compared to patients with adult onset illness, patients with early onset of their bipolar disorder (before age 19) did have children with more psychiatric difficulties.

Together, these data suggest that a parental and grandparental history of multiple different illnesses (unipolar and bipolar disorder, alcohol and substance abuse, suicide attempts, and other difficulties) conveys an increased vulnerability to early-onset bipolar disorder. More of these psychiatric problems in direct lineage relatives of patients from the United States than from Europe are also consistent with the much earlier age at onset of bipolar disorder in the United States compared to Europe.[10–12] While the total burden of psychiatric difficulties related to early age at onset, among the individual relatives, only the amount of illness in the mother was independently related to early onset.

These findings are also consistent with a large literature indicating that, starting with the child as the proband, pediatric onset bipolar disorder is more familial than attention-deficit/hyperactivity disorder or healthy controls as indicated by the increased incidence of bipolar disorder in interviewed first-degree relatives.[30] Moreover, that study also found an increased risk for other illness (such as depression, anxiety, and substance abuse disorders) in the first-degree relatives, and other studies have shown an increased familial burden in childhood versus adult onset bipolar patients.

Evidence continues to mount that bipolar disorder is highly polygenic,[31–33] and our data indirectly support the view that the genes related to these other psychiatric illnesses contribute to vulnerability to bipolar disorder[34] and, as seen here, especially its early onset. Lin et al[35] described a genetic relationship between early-onset bipolar disorder and substance abuse in both patients and their relatives. It would appear that direct links between a variety of other illnesses in relatives and early-onset bipolar disorder also deserve further investigation and analysis, although in our population only depression and "other" illness were independently significant.

As in other analyses and populations,[24,29,36] psychosocial stress in childhood was also a contributor to an early age at onset independent of family illness burden. These and other data support the view that both genetic and environmental mechanisms are at play in early-onset bipolar disorder. Epigenetic mechanisms could be involved via several different routes. The epigenetic effects of early life adversity are well established in animals and humans.[37–39] Environmentally based epigenetic effects could emanate from the stresses associated with experience of parental illness, particularly if the illness in the primary caretaker (usually the mother) was not well controlled.[40,41] New evidence also suggests that some of the effects of environmental experiences (such as stressors and exposure to substances of abuse of a parent) can be transmitted to the offspring in the absence of direct behavioral contact, presumably by epigenetic changes in

germline cells.[42–44] The effects of maternal illness on our patients could thus be conveyed in 3 ways—by genetics as well as behaviorally mediated and germline-dependent epigenetic influences.

There are multiple limitations of these data, which must be considered preliminary until replicated by other methods of direct ascertainment. All of the family history data were based on patient report and not on direct interviews of the relatives. Age at onset was also based on patient questionnaire data as well, but it correlated highly with interview-based assessment on the SCID. The data on offspring are also highly preliminary as they too were not based on direct observation, illness in 1 versus multiple offspring was not distinguished, and age at onset of illnesses in the offspring was not obtained. However, the finding that patients with early onset had more ill offspring suggests that early-onset illness not only is a vulnerability factor for a more adverse course of bipolar illness,[8–10] but also may be a marker for increased risk of multiple types of illness in the next generation. While it is possible that the populations for the United States versus Europe were not epidemiologically parallel and representative of the 2 continents, the fact that familial load of illness on both continents was related to early age at onset of bipolar disorder renders this potential limitation of less consequence. Finally, it is possible that early-onset probands could be more aware of illness in their relatives or that grandparents might be more willing to disclose a personal history of psychiatric illness when their grandchildren also became ill.

Despite the methodological limitations noted above, our data are consistent with those of other studies using more rigorous direct methods and prospective observation of offspring. Birmaher et al[2,14] found the parents with bipolar illness from the United States also had multiple other psychiatric illnesses and more than in many non-US high-risk studies.[18,20–22] These data converge with our observations of earlier onset of bipolar disorder and more complexity of illness in the offspring of bipolar parents from the United States. Axelson et al[19] also reported that multiple psychiatric illnesses were more prevalent in the offspring of a parent with bipolar disorder compared to community controls, and 74.2% of the offspring had an Axis I psychiatric diagnosis.

In addition, Birmaher and colleagues'[45] recent longitudinal follow-up data over an average duration of almost 8 years indicate a greater burden of family history–positive illness in children with bipolar illness whose course was more severe, that is, "mostly ill" as opposed to "mostly euthymic." Also, one of the risk factors for being in this "mostly ill" subgroup was the child's own early age at onset of bipolar illness.

Clinical Implications

To the extent that our data are replicated and continue to remain consistent with the findings of others in the literature, they would appear to have important implications for therapeutics and public health policy. The familial nature of bipolar disorder is no longer in doubt and appears to have both a strong genetic and epigenetic basis. This familial influence appears strong and present over multiple generations and should help turn attention away from diagnostic controversy to consideration of how best to address the very real high burden of illness in families of a bipolar proband seen here and in the literature.[14–17,19,30]

When considering children at high risk, perhaps assessment of the total grandparental as well as parental illness burden should be routinely sought and not just a perfunctory listing of the presence or not of a positive family history of bipolar disorder. If the family history of illness burden is high and multigenerational, perhaps primary prevention psychotherapeutic strategies could be considered in light of the positive outcome data on high-risk children treated preventively.[46]

More clearly, if the children are both at high familial risk and already symptomatic for depression or anxiety or prodromal for bipolar disorder or bipolar disorder not otherwise specified, active treatment such as family focused therapy would appear indicated.[47] If a child has already acquired a diagnosis of bipolar disorder, a multimodal program of family intervention and psychoeducation would be ideal to accompany targeted psychotherapeutic and pharmacotherapeutic intervention with appropriate agents. Yet, epidemiologic surveys indicate that only about 20% of adolescents with a bipolar spectrum diagnosis are in any kind of treatment.[6] Moreover, even well-diagnosed children are not always treated appropriately in the community, as 37% of the children with bipolar disorder at an average age of 11 years never received any of the recommended treatments (lithium, a mood stabilizer, or an atypical antipsychotic) at any time over the next 8 years of follow-up.[48]

In summary, parental and grandparent histories of multiple psychiatric difficulties appear highly related to an early age at onset of bipolar disorder in adults in the United States and the Netherlands and Germany. The family history burden is greater in the United States than in the European countries, and this converges with the much earlier age at onset of bipolar illness in the United States versus Europe. Psychosocial stressors in childhood are higher in the United States than Europe and are also related to early-onset bipolar disorder. Together, these genetic and environmental risk factors for early-onset illness provide further vulnerability to the next generation for multiple and varied psychiatric difficulties. Individual therapeutic approaches to those in the United States at highest risk for childhood onset bipolar disorder and wider research and public health strategies for this transgenerational conveyance of multiple psychiatric difficulties deserve immediate consideration and a long-term focus.

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Potential conflicts of interest: **Dr Post** has been on a speakers/advisory board for AstraZeneca, Sunovion, and Validus in the past 12 months. **Dr Keck** is employed by the University of Cincinnati College of Medicine and University of Cincinnati physicians; is President-CEO of the Lindner Center of HOPE; has presently been a principal or co-investigator on research studies in the last 12 months sponsored by Alkermes, AstraZeneca, Cephalon, GlaxoSmithKline, Eli Lilly and Company, Marriott

Foundation, National Institute of Mental Health (NIMH), Orexigen, Pfizer, Inc, and Shire; has been reimbursed for consulting in the past 12 months from Shire, Supernus, Otsuka, ProPhase, and Merck; and is a co-inventor on US Patent No 6,387,956: Shapira NA, Goldsmith TD, Keck, PE Jr (University of Cincinnati). Methods of treating obsessive-compulsive spectrum disorder comprises the step of administering an effective amount of tramadol to an individual, filed March 25, 1999; approved May 14, 2002, and has received no financial gain from this patent. **Dr McElroy** has been a consultant or served on an advisory board for Bracket, F. Hoffmann-La Roche, MedAvante, Naurex, Novo Nordisk, Shire, and Sunovion within the past 12 months and has received grant support from Alkermes, Cephalon, Cephalon, Forest, Marriott Foundation, Naurex, Orexigen, Shire, and Takeda within the past 12 months. **Dr Frye** has received grant support from Assurex, Janssen Research & Development, Mayo Foundation, Myriad, National Institute of Alcohol Abuse and Alcoholism, NIMH, and Pfizer; and has consulted for Janssen Research & Development, LLC, Mitsubishi Tanabe Pharma Corporation, Myriad, Sunovion, Supernus Pharmaceuticals, and Teva Pharmaceuticals. Mayo Clinic has a financial interest in Assurex and the technology referenced in this publication/presentation. **Dr Nolen** has received grants from the Netherlands Organisation for Health Research and Development, the European Union, AstraZeneca, GlaxoSmithKline, and Wyeth and has received honoraria/speaker's fees from AstraZeneca and Lundbeck (2010–2015). **Dr Suppes** received sources of funding from or medications for clinical grants from the National Institute of Mental Health, Sunovion, Elan Pharma International Limited, and VA Cooperative Studies Program; has participated in consulting agreements/advisory boards/speaking engagements for A/S H. Lundbeck, AstraZeneca, and Merck; has received continuing medical education honoraria from Medscape Education, Global Medical Education; has received royalties from Jones and Bartlett and UpToDate; and has received travel reimbursement from AstraZeneca, A/S H. Lundbeck, and Merck in the past 12 months. **Ms Leverich** and **Drs Grunze**, **Altshuler**, **Kupka**, and **Rowe** have no relevant financial interests or personal affiliations during at least the past 12 months.

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