Acta Psychiatr Scand 2009: 120: 378–385
All rights reserved
DOI: 10.1111/j.1600-0447.2009.01454.x

© 2009 John Wiley & Sons A/S
ACTA PSYCHIATRICA SCANDINAVICA

Clinical overview

Lithium response across generations

Grof P, Duffy A, Alda M, Hajek T. Lithium response across generations.

Objective: To describe and integrate observations from bipolar patients responsive to lithium stabilization and their children.
Method: Selected findings are described from the clinical and biological investigations of adults meeting research criteria for bipolar disorder and for responsiveness to lithium stabilization; and from prospective studies of the children of lithium responders and non-responders.
Results: Response to prophylactic lithium identifies a valid subtype of bipolar disorder, however the search for biological markers of lithium response, while promising, has so far remained inconclusive. Adult responders to lithium stabilization exhibit definable clinical features which are also observable in their affected children. In prospective studies the children of bipolar parents develop symptoms earlier than reported previously, with marked differences between the offspring of lithium responders and non-responders. The illness evolves in predictable clinical stages, first from non-specific sleep and anxiety disorders to mood symptoms and then, often starting in adolescence, major depressive and later activated episodes.
Conclusion: Investigating and comparing unequivocal responders and non-responders to long-term lithium treatment and their offspring is a fertile research strategy for addressing a multitude of clinical and research questions.

P. Grof[1,2], A. Duffy[1,3], M. Alda[3], T. Hajek[3,4]

[1]Mood Disorders Center of Ottawa, Ottawa, ON, Canada, [2]Department of Psychiatry, University of Toronto, ON, Canada, [3]Department of Psychiatry, Dalhousie University, Halifax, NS, Canada and [4]Prague Psychiatric Centre, 3rd Faculty of Medicine, Charles University, Prague, Czech Republic

Key words: bipolar disorders; offspring; children; lithium; long-term treatment; stabilization; clinical profile; responders; biological markers

Paul Grof MD, PhD, FRCP, Mood Disorders Center of Ottawa, Smyth Medical Centre, 202-1929 Russell Rd., Ottawa, ON, K1G 4G3, Canada.
E-mail: paul_grof@mdco.ca

Invited Paper

Clinical recommendations

- The children of lithium responsive bipolar parents may present psychopathological symptoms in childhood, earlier than reported previously in their parents.
- In the assessment and clinical management of afflicted offspring of bipolar parents it pays off to consider the whole clinical profile, not just the presenting symptoms.
- Patients stabilizing well on long-term lithium treatment represent a subgroup of bipolar disorders with particular clinical characteristics.

Additional comments

- The morbidity risks of children investigated in our studies may be elevated compared to other family studies because their bipolar parents may be more interested to involve them in this research.
- The findings reported here have been condensed to meet the space requirements. Further details can be found in the references.

Introduction

Much of the investigations summarized in this manuscript follows in the footsteps of Eric Strömgren's research, in particular his focus on longitudinal observations, lithium and genetic studies. Strömgren, one of the most outstanding European psychiatrists of all times, initiated longitudinal epidemiological studies from which he obtained vital knowledge about the natural course of psychiatric disorders. Studies investigating prospectively the clinical course in the offspring of patients with bipolar disorder (refer to as BD) now supply new information about the initial manifestations of

BD and about important parallels and differences between children, adolescents and adults.

Eric Strömgren also provided major contributions to the diagnosis and classification of psychiatric disorders. The lessons learned from bipolar offspring currently indicate a pressing need to refine the diagnostic process further, particularly in the DSM system.

Mogens Schou never failed to remind his audiences that it was Eric Stromgren who, in 1953, had drawn his attention to John Cade's report on lithium (1). Subsequently, Cade's therapeutic claim was tested and confirmed in the first psychopharmacological placebo-controlled trial on Stromgren's home territory. While Mogens Schou is universally considered the father of lithium prophylaxis, Eric Strömgren, with several publications reflecting his involvement with lithium (2), would rightfully deserve the title of its grandfather.

Eric Strömgren set the signposts and provided vital contributions to the population genetic studies of functional psychoses. Genetic research of lithium responsive mood disorders, an outgrowth of this approach, strives to advance the field by applying the progressive techniques of molecular biology to a relatively homogeneous clinical population.

Aims of the study

In this manuscript we, therefore, describe and integrate selected findings from the clinical and biological investigations of adults meeting research criteria for bipolar disorder and for responsiveness to lithium stabilization, as well as from prospective studies of the children of lithium responders and non-responders.

Material and methods

Selected findings are described from the clinical and biological investigations of adults meeting research criteria for bipolar disorder and for responsiveness to lithium stabilization; and from prospective studies of the children of lithium responders and non-responders.

Results

Lithium stabilization

Stabilization achieved through long-term lithium treatment succeeds primarily in a particular type of bipolar patients whose clinical characteristics are outlined below. For these patients it is a unique benefit that, unlike other lithium uses in psychiatry, has not been achieved by other medications (3). A complete or marked suppression of both manic and depressive recurrences takes place while therapeutic lithium concentrations are used. During long-term prevention against recurrences, we can usually determine with a high probability, if an individual patient responds specifically to the given treatment.

Many observations indicate that, of patients who are diagnosed with BD according to DSM IV, only a proportion will respond to lithium stabilization. It is therefore imperative to clarify for clinical practice which patients should receive stabilizing lithium salts as the treatment of choice. Conversely, patients whose characteristics point out that they are unlikely to benefit from lithium stabilization should be first treated with other mood stabilizers. The heterogeneity of BDs has been well recognized for 30 years (4), but has not yet been sufficiently incorporated into psychopharmacological thinking.

The observation that numerous patients with recurrent manic-depressive illness could be stabilized on a simple element – lithium – made a significant contribution to profound changes in psychiatric thinking. During the following decades the point of gravity in psychiatry moved from psychosocial to neurobiological, from psychoanalysis to pharmacotherapy, and the diagnostic boundaries of mood disorders have been markedly broadened.

Children of lithium responders

Studying children of bipolar parents has turned out to be a fruitful strategy. Bipolar disorder clusters in families and first-degree relatives share an 8–12 fold risk of bipolar disorder compared to the general population. Intriguing findings have been emerging from the prospective studies of the children of bipolar parents, particularly from the scrutiny of the offspring of lithium responders.

Prior to 1970 a common recommendation to women with BD was not to have children and many affected women had actually followed this advice (5). But with the widespread use of lithium the observation of a larger number of children became possible: now dealing with a treatable malady, women became mothers more readily and later started bringing their symptomatic children for assessment and care. Stabilized parents assumed we would be able to help their children in the same way.

Fifteen years ago, our research group led by Dr Anne Duffy embarked on prospective studies of these offspring (6–13). Parents participated in Mood Disorders Research Program and their bipolar clinical profile was well captured. To

qualify, each parent had to be either an unequivocal responder or non-responder to stabilizing lithium treatment, in order to reduce bipolar heterogeneity, and had to have a psychiatrically unaffected partner.

Starting at 8 year of age, the children have been assessed and diagnosed by an independent team blind to the parent's clinical profile, and then seen prospectively either when they become symptomatic or annually. Full information about the child's infant years was recovered from parents. A control group of children born of parents free from psychiatric illness was investigated in parallel.

The longitudinal study of offspring of bipolar parents is a productive strategy for charting the clinical beginnings of the illness, identifying the sources of vulnerability and protection, uncovering the interplay of important pathophysiological factors, exploring treatment responses and investigating the onset and progression of bipolar illness not yet contaminated by the burden of illness and interventions.

Different beginnings of bipolar disorder?

The description of the course of bipolar illness available from the major studies of adults used to picture the mean onset of episodes in the mid 30s (14) and prepubertal children were spared of symptoms; no non-specific or specific psychopathological antecedents were noted before adolescence. Similarly, when interviewed about their childhood, adult lithium responders described their prepubertal life as free of psychiatric problems (15). These reports were usually verified by their relatives and clinical records. But the new findings obtained prospectively from their offspring, and summed up here, present a very different picture.

First, the children of bipolar parents – lithium responders and non-responders – become ill not only earlier but also differently than expected from the previous observations of their parents. Compared to the offspring of well parents, their morbidity is increased, but does not initially present as major mood episodes (13). The first manifestations in childhood are non-specific and include various presentations of anxiety and sleep disorders. This increased risk of non-mood psychopathology in those developing mood disorders is in agreement with several other studies (16, 17). However, this non-specific psychopathology appearing at an early age does not mean the condition termed as pediatric BD (18, 19). On the other hand, it is also important to note that the vast majority of offspring who remained completely well throughout childhood and adolescence have stayed well into early adulthood.

Second, there are qualitative differences between the offspring of lithium responders and non-responders. The difficulties of offspring of lithium responders, whether non-specific or specific, run an episodic course and in adolescence present mostly as mood disorders. Conversely, the offspring of non-responders show either partially remitting or non-remitting fluctuating course of illness and not infrequently manifest cluster A traits (social inhibition, odd thinking) and cognitive problems diagnosed as attentional problems and learning disabilities (9).

Third, while investigating offspring of bipolar parents, Duffy discovered that BD evolves in stages. If the child becomes afflicted, the initial non-specific expressions – childhood sleep and various anxiety disorders – evolve around puberty into minor depressive symptoms and oversensitivity to stress. The onset of major depressive episodes follows, starting in mid-adolescence, while activated mood episodes – hypomanic or manic – trail several years later. The pre-existing anxiety markedly increases the risk of later mood episodes (Fig. 1). The illness propensity may manifest for the first time at any of these stages, but subsequent manifestations then follow the expected sequence. Other high risk studies have reported observations that are in keeping with these clinical stages (20, 21).

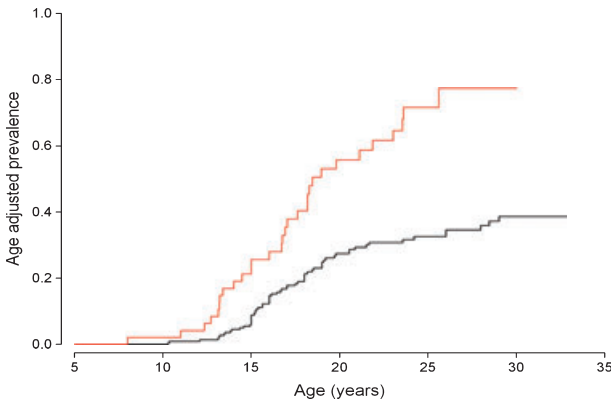

Fig. 1. Risk of onset of mood disorder increased by pre-existing anxiety disorder. Survival analysis. A combined sample of Duffy et al. (The early course of bipolar disorder in a prospective study of high-risk offspring. Br J Psychiatry 2009, in press) and Grof et al. (Children at high risk for bipolar disorders, Psychiatrie, 2009; in print), 307 offspring of a bipolar parent. Red: offspring with anxiety disorder preceding mood disorder; Black: offspring with mood disorder without preceding anxiety disorder.

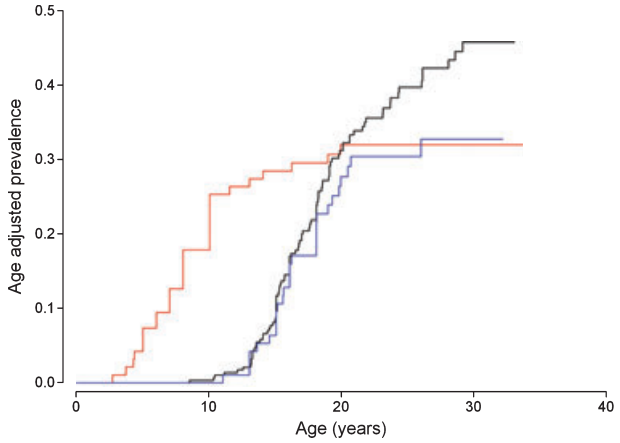

Fig. 2. Risk of onset of mood disorder in relation to anxiety disorder or substance abuse. Survival analysis. A combined sample of Duffy et al. (The early course of bipolar disorder in a prospective study of high-risk offspring. Br J Psychiatry 2009, in press) and Grof et al. (Children at high risk for bipolar disorders, Psychiatrie, 2009; in print). Black: age at onset of mood disorder in the whole sample; Red: age at onset of anxiety disorder in subjects who experienced mood disorder; Blue: age at onset of substance abuse in subjects who experienced mood disorder.

Consistent with adult studies, substance use disorders in the offspring start to appear in adolescence, in our cohort at the same time as, or following, the first major mood episode (Fig. 2). Already having a mood disorder nearly doubled the age-adjusted risk of a substance use disorder (mostly alcohol and/or cannabis). It must be clarified that in children of parents who are not affected with BD, childhood anxiety, sleep or minor mood disturbances should not be considered as predictors of BD (22).

Finally, pilot data indicate that adolescents who develop recurrences and require stabilizing treatment can respond well to monotherapy with a stabilizer tailored to their clinical profile (11). The accomplishment of the chosen mood stabilizer depends on the nature of the patient's clinical course (episodic vs. non-episodic) and the response to the same stabilizer in the patient's parent. These observations indicate that a useful diagnostic and treatment formulation of adolescents should include a careful assessment of the patient's clinical course and of family history of disorders and treatment responses. They also contradict the conviction that adolescents, as a rule, suffer from disorders with complex comorbidities requiring polypharmacy.

These landmark investigations of the offspring of parents with BD now proceed to firm up the findings on other cohorts and to integrate findings from clinical, genetic, biological and psychosocial research in a unified bipolar model.

Practical implications

Finding non-specific psychopathology in offspring of a parent with BD has important consequences for later development. Having such a parent is the strongest single risk factor for mood disorders later and the majority of those offspring who manifest anxiety disorders become affected with a major mood disorder, on average 8 years later (12). Fortunately, the majority of offspring of bipolar parents remain unaffected in youth.

Furthermore, it is important to evaluate young patients with mood symptoms for relevant family history. When a family history and a possible stage of BD are overlooked, the early manifestations of latent BD are often treated as the presenting problem, with polypharmacy including stimulants, antidepressants and psychotherapy. This approach, while not part of our treatment, can have harmful consequences (23) including a higher risk of suicide and of paradoxical response to antidepressants (24).

In addition, longitudinal investigations of offspring of lithium responsive parents do not support either an association of this condition with ADHD or with a so called 'pediatric bipolar disorder' (18, 19, 25). We did not observe such symptomatic cluster in either of our cohorts. This syndrome is more likely a non-specific predictor of variable psychiatric outcomes and not an early form of BD (11, 13).

Adult responders and their offspring: differences and similarities

When contrasting lithium-responsive parents and their offspring, the main difference is the information available about childhood. While the adults described in retrospect that their illness started with depressions and manias in adolescence or adulthood, the prospective observations of their offspring finds that a sizable proportion actually begin having non-specific problems much earlier. This difference may be either an artifact, or real, or a combination.

As for the artifact, the adults may have forgotten or repressed the symptoms from childhood, particularly after experiencing later major episodes of abnormal mood. In earlier studies adult patients were usually identified for research through their hospitalization, and they provided retrospective information about the onset and the previous course of illness. The fallibility of recall has been well established. Furthermore, as the interviewers did not expect symptoms in childhood, they may not have been sufficiently sensitive to detect the non-specific symptoms.

But the re-interviews of adult lithium responders, their parents and older siblings do not support a simple 'artifact' of recall or repression. Further, the discrepancy between the pristine, symptom-free childhood of previous generation of lithium-responders and earlier harbinger symptoms in the offspring may also have some real roots. Klerman, for example (26), and World Health Organization reports also indicate a steady increase in mood disorders in subsequent generations. The impact on a child growing up with a bipolar parent also has to be considered.

There are, on the other hand, striking similarities between parents and their offspring in both lithium responsive and non-responsive families. First, the characteristics of the clinical course of children mirror the ill parent. If the affected parent experienced episodic, fully remitting course, so do the ill children. Similarly, parents with a non-episodic course and residual symptoms have offspring with chronic or fluctuating, non-episodic psychiatric problems. More important, the same type of clinical course for the parent and the afflicted children is observed regardless of whether the presenting psychopathology is non-specific, or whether the manifestations are full-fledged depressive or manic episodes.

Second, evidence is growing that when the children require long-term stabilizing treatment, they appear to respond to the same mood stabilizer as their parent, rather than responding to the standard treatment that is prescribed according to their presenting symptoms (10, 11). The over-reliance on symptom-based diagnosis and the neglect of clinical profile, including correct family history, may explain why so many depressed adolescents are presumed to be treatment resistant.

These similarities strongly suggest that all the varied psychopathological manifestations in offspring and their lithium-responsive parents and all the different stages of BD may be actually arising from one, comparable brain dysregulation.

The search for biological markers

The observed remarkable responses to stabilizing treatment with a simple ion had generated hope for an uncomplicated laboratory test of lithium response. As many new laboratory techniques were then introduced into biological psychiatry, they were also applied to revealing lithium's mode of action and response.

But many studies struggled with the methodological complexities of the mission. Among the main obstacles has been the correct identification of responders and non-responders to stabilizing lithium. As the natural course of BD is capricious, individually highly variable, and patients waver in their compliance with long-term medication, such a research task is challenging. To obscure things, the patients may also benefit from anti-manic, anti-psychotic, anti-aggressive, anti-suicidal or augmenting effect of lithium, without ever stabilizing over the long-term.

We also placed our hopes on biological markers and over 20 years performed a series of systematic investigations comparing unequivocal responders and non-responders to lithium stabilization. After correcting for confounding variables, many laboratory findings emerged as negative, but a few differences became apparent. We found characteristic neuroendocrine responses in lithium responders (27, 28). At baseline, healthy controls and symptom-free, remitted responders were indistinguishable, but only responders exhibited significantly different responses after 3 weeks of lithium administered to both groups. These changes in responders were compatible with a serotonin or endorphin trait dysfunction. Lithium responders also differed significantly from healthy and psychiatrically ill controls in the MNS blood groups (29). Unfortunately, these differences have only a limited practical value.

Many others attempted to discover a laboratory marker of lithium response, with similar outcomes. From a wealth of reports, we have included a few illustrations: lithium transport in red blood cells (30), an RBC/plasma lithium ratio (31), urinary lithium excretion (32), platelet monoaminoxidase activity (33), urinary MHPG and other expressions of central amine metabolism (34), serum calcium and magnesium (35, 36), average evoked potentials (37, 38) and HLA antigens (39). As one example of recent studies, an investigation by Kruger et al. (40) comparing rCBF in valproate responders, lithium responders and their unaffected relatives showed significant, possibly heritable differences between the two patient groups.

The search for biological markers of response to a simple lithium ion has turned out to be surprisingly complex. Even after several decades of intense explorations, a laboratory marker of lithium response appears elusive.

Genetic culprits

The genetic studies of lithium response merit mentioning separately because they offer great promise and have been expanding recently (41–45). There are good reasons for optimism: Both BD and lithium response cluster in families (46), the illness itself appears to have the strongest genetic

contribution of all psychiatric disorders and the responders to lithium stabilization are a relatively homogeneous bipolar subtype (4). Furthermore, molecular genetics has already proven its usefulness by major discoveries in neurology and other branches of medicine.

During the past two decades DNA of lithium-responsive probands and their families have been investigated in linkage and association studies and in genome scans. Some meta-analyses of genetic findings in bipolar patients also included a proportion of lithium responders (47). The findings overall suggest that the bipolar subgroup responsive to long-term lithium treatment has a genetic contribution that is distinct from other subtypes of bipolar patients. In families of lithium-responsive probands, we have found neither support for previously reported linkages to chromosomes 13 and 22 that have been observed in families with a high prevalence of psychotic symptoms, nor linkages to regions on chromosome 18 that have been reported in bipolar families with comorbid panic disorder, high rates of bipolar II disorder and rapid cycling. The observations available so far indicate that patients with these clinical characteristics stabilize preferentially on atypical neuroleptics and lamotrigine respectively (15, 48). Studies comparing lithium responders and non-responders have also attracted attention to the serotonin transporter gene, inositol monophosphatase gene and mitochondrial gene XBP1. Within the assigned space we cannot do justice to this promising, quickly expanding area and are referring the reader to a comprehensive overview that also contains the references to the above mentioned studies (49).

Clinical profile of lithium responders

While we searched extensively for biological explanations of lithium response, the analyses of the accumulated clinical database revealed a characteristic clinical profile of excellent responders (50–52). Coincidentally, the first presentation of our results on multivariate analyses took place on Eric Strömgren's home turf, at the Institute in Risskov (50). The clinical features that emerged were later confirmed independently in controlled clinical studies (48) as well as in other naturalistic studies (53, 54) and can be summarized as follows.

The most useful indicator of future success with lithium stabilization is the clinical profile of the bipolar patient (55). The fully remitting course of illness is the strongest predictor, and is supported by a family history of episodic bipolar and depressive disorders, and no comorbidity with other psychiatric disorders. During remissions, the future responders not only return to their premorbid work and family functioning, but they are also free of any residual symptoms, affective or non-affective. Concomitant comorbidity with other psychiatric disorders in excellent responders does not exceed that expected in the general population. Provided the above features from the patient's history are present, the symptoms of classical depression and mania in acute episodes also aid in the prediction of response.

Patients with this characteristic profile who need stabilizing treatment benefit from lithium as the monotherapy of choice. An excellent, sustained response to lithium prophylaxis is one of the most gratifying outcomes a psychiatrist may experience.

To estimate in practice whether a particular patient with a recurrent mood disorder is likely to stabilize well on lithium, it is vital to obtain the information about the patient's clinical profile comprehensively and to interpret it carefully. While the quality of remissions is especially important, many psychiatrists must first learn to assess it correctly because psychiatric training has been focusing on identifying acute psychopathology, not its complete absence. The lack of residual symptoms and the good quality of remission can be also measured by MMPI profile that differs significantly between responders and non-responders (56) as well as between their children (57).

There are three recent studies focusing on detecting the clinical predictors of lithium response. Kleindienst et al. (58) analyzed data from 43 suitable clinical trials of lithium by meta-analytic aggregation based on a random effects model and effect size measure. The authors concluded that none of the investigated variables alone actually predicted lithium response which seemed to be related to a multitude of variables. They felt that past history of a patient predicts the response to prophylactic lithium better than the patient's presenting clinical picture. Two analyses of the longitudinal observations gathered by the International Group for the Study of Lithium-Treated Patients (59) have demonstrated that in bipolar patients with mainly classical profile the response is stable over time. When tested with models that account for the interdependence of clinical features, the predictors that emerged are essentially compatible with the described clinical predictors.

Discussion

The history of the use of lithium in psychiatry has been marked by delays, misunderstandings and controversies and the research of response to lithium stabilization has appeared as methodolog-

ically tricky, challenging and complicated as the history of lithium use itself. A massive body of investigations attempted to discover a biological marker of lithium response and some promising linkages have been recently emerging from genetic studies. However, if we want to identify patients who will likely benefit from lithium stabilization, we still need to base this on the patient's clinical profile.

Most intriguing have been the prospective studies of offspring of lithium responders. The observations indicate that early manifestations of BD may now actually start in childhood, with non-specific symptoms, which evolve in a series of predictable clinical stages. The patient may experience the first manifestations during any stage, but then proceeds through the anticipated sequence.

In combination with the new studies of pre-psychotic states (60), these findings challenge some of the historically based assumptions of diagnosing, classifying and treating primarily on the basis of psychopathological symptoms.

The third generation – grandchildren of the adult lithium responders – is now emerging and may offer new insights. As measurements showed that only a few mothers pass lithium into their milk in concerning amounts, we now follow a cohort of children that have been breastfed from their first day of life by lithium-treated mothers. A body of animal research indicates that the reactivity of the brain can be changed profoundly by nutritional changes imprinted during the first weeks of life. A systematic follow-up of this generation might offer some new insights, perhaps even into primary prophylaxis.

Declaration of interests

None of the authors has any conflict of interest in connection with the content of this manuscript.

References

1. Cade J. Lithium salts in the treatment of psychotic excitement. Med J Aust 1949;**36**:349–352.
2. Schou M, Juel-Nielsen N, Stromgren E, Voldby H. Lithium in therapy of manic psychoses.(in Danish). Ugeskr Laeger 1955;**117**:93–101.
3. Grof P. Has the effectiveness of lithium changed? Impact of the variety of lithium's effects. Neuropsychopharmacol 1998;**19**:183–188.
4. Alda M, Turecki G, Jaitovitch-Groisman I et al. Clinical and genetic heterogeneity of bipolar disorder. Bipolar Disord 8 2006;**8**(Suppl. 1):60.
5. Grof P, Robbins W, Alda M et al. Protective effect of pregnancy in women with lithium-responsive bipolar disorder. J Affect Disord 2000;**61**:31–39.
6. Duffy A, Alda M, Kutcher S, Fusee C, Grof P. Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. Am J Psychiatry 1998;**155**:431–433.
7. Duffy A, Alda M, MacQueen G et al. A comprehensive longitudinal study of the offspring of lithium responsive and lithium non-responsive bipolar parents. Acta Psychiatr Scand Suppl 2004;**110**:10.
8. Duffy A, Alda M, Kutcher S et al. Prospective longitudinal follow-up study of the offspring of lithium responsive and lithium non-responsive bipolar parents. Bipolar Disord 2001;**3**(Suppl. 1):34.
9. Duffy A, Alda M, Crawford L, Milin R, Grof P. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. Bipolar Disord 2007;**9**:828–838.
10. Duffy A. Does bipolar disorder exist in children? A selected review. Can J Psychiatry 2007;**52**:409–417.
11. Duffy A, Alda M, Milin R, Grof P. A consecutive series of treated affected offspring of parents with bipolar disorder: is response associated with the clinical profile? Can J Psychiatry 2007;**52**:369–375.
12. Duffy A, Alda M, Hajek T, Grof P. The early course of bipolar disorder in a prospective study of high-risk offspring. Br J Psychiatry 2009;**195**:1–3.
13. Duffy A, Alda M, Hajek T, Sherry S, Grof P. Early stages in the development of bipolar disorder. J Affect Disord 2009;doi:10.1016/j.jad.2009.05.022.
14. Angst J, Baastrup PC, Grof P, Hippius H, Poldinger W, Weiss P. Clinical course of affective disorders. Psychiatry 1973; **76**:489–500.
15. Grof P. Selecting effective treatments for bipolar disorders. J Clin Psychiatry 2003;**64**(Suppl. 5):53–61.
16. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H-L, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry 2003;**60**:709–717.
17. Eaves L, Silberg J, Erkanli A. Resolving multiple epigenetic pathways to adolescent depression. J Child Psychol Psychiatry 2003;**44**:1006–1014.
18. Geller B, Zimerman B, Williams M, DelBello MP, Frazier J, Beringer L. Phenomenology of prepubertal and early adolescent bipolar disorder: examples of elated mood, grandiose behaviours, decreased need for sleep, racing thoughts and hypersexuality. J Child Adolesc Psychopharmacol 2002;**12**:3–9.
19. Geller B, Tillman R, Bolhofner K, Zimerman B. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. Arch Gen Psychiatry 2008;**65**:1125–1133.
20. Akiskal HS, Downs J, Jordan P, Watson S, Daugherty D, Pruitt DB. Affective disorders in referred children and younger siblings of manic-depressives: mode of onset and prospective course. Arch Gen Psychiatry 1985;**42**:996–1003.
21. Hammen C, Burge D, Burney E, Adrian C. Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. Arch Gen Psychiatry 1990;**47**: 1112–1117.
22. Carlson GA, Weintraub S. Childhood behavior problems and bipolar disorder – relationship or coincidence? J Affect Disord 1993;**28**:145–153.
23. Reichart CG, Nolen WA. Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis. J Affect Disord 2004;**78**:81–84.
24. Duffy A. Lithium treatment in children and adolescents: a selected review and integration of research findings. In:

Bauer M, Grof P, Muller-Oerlinghausen B, eds. Lithium in neuropsychiatry: the comprehensive guide. London, UK: Taylor & Francis Book Ltd, 2006:193–206.
25. Biederman J, Mick E, Prince J et al. Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder. J Child Adolesc Psychopharmacol 1999;**92**:47–256.
26. Klerman GL, Lavori P, Rice J et al. Birth-order cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. Arch Gen Psychiatry 1985;**42**:689–693.
27. Grof E, Grof P, Brown GM, Downie S. Lithium effects on neuroendocrine function. Prog Neuropsychopharmacol Biol Psychiatry 1984;**85**:41–546.
28. Grof E, Grof P, Brown GM. Investigations of lithium effects on neuroendocrine function in man. In: Birch MJ, ed. Lithium: inorganic pharmacology and psychiatric use. Oxford: IRL Press Ltd, 1987:177–181.
29. Alda M, Grof P, Grof E. MN blood groups and bipolar disorder: evidence of genotypic association and Hardy-Weinberg disequilibrium. Biol Psychiatry 1998;**44**:361–363.
30. Upadhyaya AK, Varma VK, Sankaranayanaran A. Lithium in prophylactic therapy of manic-depressive illness:biochemical correlates of response. Biol Psychiatry 1985;**20**:202–205.
31. Mendels J, Fraser A, Baron J. Intraerythrocyte lithium ion concentration and longterm maintenance treatment. Lancet 1976;**1**:966.
32. Serry M. Lithium retention and response. Lancet 1969; **1**:1267–1268.
33. Sullivan JL, Cavenar JO, Maltbie A. Platelet-monoaminooxidase activity predicts response to lithium in manic-depressive illness. Lancet 1977;**2**:1325–1327.
34. Carroll BJ. Prediction of treatment outcome with lithium. In: Cooper TN, Gershon S, Kline N et al., eds. Lithium, controversies and unresolved issues. Amsterdam: Excerpta Medica, World Congress Lecture Series, 1979:171–197.
35. Carman JS, Post RH, Teplitz TA, Goodwin FK. Divalent cations in predicting antidepressant response to lithium. Lancet 1974;**21**:454.
36. Goodwin FK, Post R, Dunner DL, Gordon EK. Cerebrospinaal amine metabolites in affective illness. Am J Psychiatry 1973;**130**:73–79.
37. Buchsbaum M, Goodwin F, Murphy D. AER in affective disorders. Am J Psychiatry 1971;**128**:19–25.
38. Baron M, Gershon ES, Rudy V, Jonas WZ, Buchsbaum M. Lithium carbonate response in depression. Arch Gen Psychiatry 1975;**32**:1107–1111.
39. Maj M, Arena F, Loverno N et al. Factors associated with response to lithium prophylaxis in DSM III major depression and bipolar disorder. Pharmacopsychiat 1985; **18**:309–313.
40. Kruger S, Alda M, Young LT, Goldapple K, Parikh S, Mayberg H. Risk and resilience markers in bipolar disorder: brain responses to emotional challenge in bipolar patients and their healthy siblings. Am J Psychiatry 2006; **163**:257–264.
41. Rybakowski JK, Suwalska A, Skibinska M et al. Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. J Pharmacopsychiat 2005;**38**: 186–170.
42. Rybakowski JK, Suwalska A, Czrski PM, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Hauser J. Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. Pharmacol Rep 2005;**57**:124–127.
43. Serretti A, Lilli R, Mandelli L, Lorenzi C, Smeraldi E. Serotonin transporter gene associated with lithium prophylaxis in mood disorders. Pharmacogenomics J 2001; **1**:171–177.
44. Turecki G, Grof P, Grof E et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry 2001;**6**:570–578.
45. Alda M, Turecki G, Sun X et al. Combining clinical and biochemical phenotypes in mapping susceptibility genes for bipolar disorder. Am J Med Genet (Neuropsychiatric Genetics) 2006;**141**:B713.
46. Grof P, Duffy A, Cavazzoni P et al. Is response to prophylactic lithium a familial trait? J Clin Psychiatry 2002; **63**:942–947.
47. Segurado R, Detera-Wadleigh SD, Levinson DF et al. Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. Am J Hum Genet 2003;**73**:49–62.
48. Passmore MJ, Garnham J, Duffy A et al. Phenotypic spectra of bipolar disorder in lithium responders vs. lamotrigine. Bipolar Disord 2003;**5**:110–114.
49. Alda M, Grof P, Zvolsky P. Genetic factors and response to lithium treatment. In: Bauer M, Grof P, Mueller-Oerlinghausen B, eds. Lithium in neuropsychiatry:the comprehensive guide. London: Informa, 2006:423–432.
50. Grof P, Lane J, MacCrimmon D et al. Clinical and laboratory correlates of the response to long-term lithium treatment. In: Stromgren E, Schoua M, eds. Origin, prevention and treatment of affective disorders. London: Academic Press, 1979:27–40.
51. Grof P, Hux M, Grof E, Arato M. Prediction of response to stabilizing lithium treatment. Pharmacopsychiat 1983;**16**: 195–200.
52. Grof P, Alda M, Grof E, Fox D, Cameron P. The challenge of predicting response to stabilising lithium treatment. The importance of patient selection. [Review]. Br J Psychiatry 1993;**163**(Suppl. 21):16–19-19
53. Abou-Saleh MT. Who responds to prophylactic lithium therapy? Br J Psychiatry 1993;**21**(Suppl.):20–26.
54. Maj M. Clinical prediction of response to lithium prophylaxis in bipolar patients: a critical update. Lithium 1992;**3**:15–21.
55. Grof P. Selecting effective long-term treatment for bipolar patients: monotherapy and combination therapy. J Clin Psychiatry 2003;**64**(Suppl. 5):53–61.
56. Lane J, Grof P, Daigle L, Varma R. The Minnesota multiphasic personality inventory in the prediction of response to lithium stabilization. In: Dufour H et al., eds. The prediction of lithium response. Marseille: University of Marseille, 1983:215–220.
57. Demidenko N, Grof P, Alda M, Deshauer D, Duffy A. MMPI as a measure of subthreshold residual psychopathology among the offspring of lithium responsive and non-responsive bipolar parents. Bipolar Disord 2004;**6**:1–6.
58. Kleindienst N, Engel R, Greil W. Which clinical factors predict response to prophylactic lithium? A systematic review for bipolar disorders. Bipolar Disord 2005;**7**:404–417.
59. Berghoefer A, Alda M, Mazda A et al. Long-term effectiveness of lithium in bipolar disorder: a multicenter investigation of patients with typical and atypical features. J Clin Psychiatry 2008;**69**:1860–1868.
60. McGorry P, Killackey E, Yung A. Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry 2008;**7**:148–156.