

EUR Research Information Portal

Cyclothymia or unstable mood disorder? A systematic treatment evaluation with valproic acid

Published in:

Journal of Applied Research in Intellectual Disabilities

Publication status and date:

Published: 01/01/2001

DOI (link to publisher):

[10.1046/j.1468-3148.2001.00063.x](https://doi.org/10.1046/j.1468-3148.2001.00063.x)

Document Version

Publisher's PDF, also known as Version of record

Citation for the published version (APA):

Verhoeven, W., & Tuinier, S. (2001). Cyclothymia or unstable mood disorder? A systematic treatment evaluation with valproic acid. *Journal of Applied Research in Intellectual Disabilities*, 14, 147-154. <https://doi.org/10.1046/j.1468-3148.2001.00063.x>

[Link to publication on the EUR Research Information Portal](#)

Terms and Conditions of Use

Except as permitted by the applicable copyright law, you may not reproduce or make this material available to any third party without the prior written permission from the copyright holder(s). Copyright law allows the following uses of this material without prior permission:

- you may download, save and print a copy of this material for your personal use only;
- you may share the EUR portal link to this material.

In case the material is published with an open access license (e.g. a Creative Commons (CC) license), other uses may be allowed. Please check the terms and conditions of the specific license.

Take-down policy

If you believe that this material infringes your copyright and/or any other intellectual property rights, you may request its removal by contacting us at the following email address: openaccess.library@eur.nl. Please provide us with all the relevant information, including the reasons why you believe any of your rights have been infringed. In case of a legitimate complaint, we will make the material inaccessible and/or remove it from the website.

Brief Report

Cyclothymia or Unstable Mood Disorder? A Systematic Treatment Evaluation with Valproic Acid

Willem M. A. Verhoeven

*Vincent van Gogh Institute for Psychiatry, Stationsweg 46, 5803 AC Venray, and
Erasmus University, Faculty of Medicine and Medical Sciences, Dr. Molewaterplein 50,
3015 GE Rotterdam, the Netherlands*

Siegfried Tuinier

*Vincent van Gogh Institute for Psychiatry, Stationsweg 46, 5803 AC Venray, the
Netherlands*

Paper accepted 13 March 2001

Cyclic changes in behaviour and mood which do not meet the criteria for bipolar affective disorder have been reported in people with intellectual disability (ID) since the beginning of the twentieth century. The present study postulates a functional disturbance of unstable mood disorder in such cases of an episodic pattern of disturbed behaviour, mood and anxiety. Since symptoms of hypomania or major depression are not observed in these individuals, the unstable mood disorder cannot be regarded as being part of the bipolar spectrum, although it resembles cyclothymia in some aspects. In this pilot study, 28 subjects with ID were treated with valproic acid in dosages leading to a mean plasma concentration of 63 mg L^{-1} . A marked and sustained improvement was achieved in 68% of subjects in terms of both behaviour stability, and a reduction of symptoms in the mood, anxiety and motor domains.

Introduction

Ever since the involvement of psychiatry in the care of people with intellectual disability (ID), descriptions of episodic mood changes which do not meet the criteria for a major affective disorder have been published. At the beginning of the twentieth century, the French psychiatrist Sollier (1901) described sudden mood swings associated with anxiety, changes in motor activity and challenging behaviours which could be distinguished from manic episodes. Similar observations have been made in the German literature. For example, Bumke (1929) reported rapid changes in affect and behaviour which were considered to be a specific psychopathological entity. Emotional instability characterized by rapid mood changes, irritability and dysphoria has also clearly been delineated from manic depressive illness in British studies (Duncan 1936). In the more recent literature, Gualtieri (1991) also emphasized the resemblance to affective disorders in organic brain syndromes which do not easily meet the criteria for DSM-IV classification. Such conditions have been described under several headings, such as atypical bipolar syndromes, mixed states with features of depression and mania, unipolar mania,

cyclothymia, dysthymia, and rapid cycling bipolar disorders (Ruedrich 1993; Akiskal 1994, 1996; Vanstraelen & Tyrer 1999).

In line with the original descriptions from the western European tradition, Meins (1994) concluded from factor analytic studies that a symptom cluster characterized by mood swings, irritability, impulsivity, aggression and self-injury can be identified in subjects with ID. Matson *et al.* (1991) made comparable observations in a study involving 506 people with ID: a factor emerged including rapid mood changes, crying, periods of sudden motor or vocal activities, and episodic aggression dysregulation. Finally, in a review by Einfeld & Aman (1995), it was noted that emotional lability as a factor is either accompanied by aggressive and impulsive behaviour, or by anxious symptoms and self-injury.

Therefore, on the basis of these considerations, the present authors recently postulated the concept of unstable mood disorder in cases characterized by a cyclic alteration of behaviour associated with an episodic pattern of disturbed mood and/or anxiety (Verhoeven & Tuinier 1999, 2000).

The present pilot study describes the effects of valproic acid treatment on individuals with ID suffering from unstable mood disorder.

Subjects and methods

Subjects were recruited from a sample of 248 individuals, living in more than 20 different residential settings, who were referred for neuropsychiatric evaluation to one of the present authors (W.M.A.V.) over a period of 3 years. The functional disturbance of unstable mood disorder was ascertained primarily on the basis of rapid or episodic fluctuations in behaviour in general, and secondarily, on the presence of prominent mood deviations eventually accompanied by dysphoria, irritability, anxieties and/or motor signs such as hyperactivity, stereotypies, self-injuries and aggression. Subjects with a clear neuropsychiatric diagnosis such as uni- or bipolar major affective disorder, psychotic disorder, obsessive compulsive disorder, epilepsy-related behaviour dyscontrol or challenging behaviours within the context of an established psychiatric aetiology were excluded. In no case was any manifestation of hypomania or major depression noticed.

This selection procedure resulted in a sample group of 28 subjects with ID in the mild to severe range. All individuals in the group had a long history of episodic changes in behaviour and affect. Treatment with various psychotropic drugs, such as antipsychotics, antidepressants and anxiolytics, as well as numerous behavioural interventions, had not resulted in a sustained reduction or prevention of their challenging behaviours, which comprised aggression, self-injury, irritability and agitation. The main characteristics of the subjects are presented in Table 1. The specific aetiologies included trisomy 21 ($n = 2$), incomplete trisomy 15 ($n = 1$), congenital hypothyroidism ($n = 1$) and microcephaly ($n = 1$). Neurological or somatic comorbidity was present in 11 subjects, while a psychiatric diagnosis had been previously established according to the medical record in 20 participants.

All subjects were examined in their residential settings and examples of behavioural abnormalities were videotaped in all cases. A history was obtained from the subjects' interdisciplinary team members as well as from the medical records, including laboratory test results, psychological assessments and behavioural data. There was a recent clinical genetics work-up for all subjects.

Table 1 Characteristics of the subjects ($n = 28$)

<i>Characteristic</i>	<i>Number</i>
<i>Age and sex</i>	
Sex:	
male	18
female	10
Age (years):	
mean	37.3
range	18–66
<i>Aetiology</i>	
Unknown	16
Perinatal complications	6
Encephalitis postvaccinalis	1
Specific syndromes	5
<i>Neurological or somatic comorbidity</i>	
Epilepsy	3
History of epilepsy	5
Tardive dyskinesia	1
Renal transplantation	1
Traumatic cataract	1
<i>Previous psychiatric diagnoses</i>	
Mood disorder	12
(Atypical) autism	4
Psychotic disorder	3
Panic disorder	1
<i>Current medication</i>	
Anticonvulsants for epilepsy	3
Anticonvulsants for behavioural control	2
Antipsychotics	20
Antidepressants	6
Anxiolytics	8

Standard clinical interviews could not be used since most of the subjects were not sufficiently verbally competent. Diagnostic assessments relied heavily on the behavioural components of psychiatric disorders. Diagnoses of a probabilistic nature were established during multidisciplinary consensus meetings and were based on the ICD-10 clinical descriptions and diagnostic guidelines (WHO 1992). After having defined the specific components of each subject's functional disturbance, the frequency and intensity of target symptoms from the mood, anxiety and motor domains were monitored at biweekly intervals by staff members applying visual analogue scales. Based on these data, a baseline-controlled design was followed and the general treatment effect was assessed during multidisciplinary meetings at 3-month intervals by using the Clinical Global Improvement Scale (CGIS; Guy 1976). The CGIS comprises a clinician rating of the individual treatment effect and its items are scaled from (1) 'very much improved' to (7) 'very much worse'. A final evaluation was made after 6 months ($n = 7$) or one year.

Concomitant medication was stable for at least 3 months prior to the beginning of the experiment and was kept unchanged over the first 12 weeks of treatment. Co-medication (except for anticonvulsants in the three subjects with epilepsy) was tapered off in case

of a positive therapeutic response. The tapering-off period was between 6 weeks and 3 months depending on dosage and duration of pharmacological treatment.

In all subjects, treatment with valproic acid started at a daily dosage of 300 mg and this was subsequently increased over a period of 6 weeks. Dosage adjustments were made to obtain a plasma concentration of at least 60 mg L⁻¹ unless a response was clearly achieved at a lower level. The guidelines of the Dutch Association of Psychiatry recommend a plasma concentration of valproic acid of 60–80 mg L⁻¹ for maintenance therapy for bipolar affective disorder.

Results

Valproic acid was prescribed in 28 subjects within a dose range of 300–3000 mg day⁻¹ (mean ± SD = 1345 ± 619 mg day⁻¹), leading to a mean plasma concentration of 63 mg L⁻¹ (SD = 17 mg L⁻¹; range = 20–96 mg L⁻¹). No major side-effects were observed. Premature discontinuation of treatment did not have to be considered in any of the subjects because of behavioural deterioration, intercurrent illnesses or pharmacokinetic interactions. A follow-up period of at least one year was achieved in 21 subjects. In the other seven subjects, this period comprised 6 months only. The dosage of valproic acid was kept unchanged over the total follow-up period in all the subjects.

As assessed with the CGIS, a moderate to marked improvement (much and very much) was observed in 19 participants. As a rule, the improvement was comprised of a stabilization of behaviour and mood, as well as a reduction of symptoms belonging to the mood, anxiety and motor domains (Table 2). Minimal changes or no improvement at all were noted in nine subjects (Table 3).

In three subjects using carbamazepine, the addition of valproic acid resulted in a marked improvement without changes in plasma concentrations of carbamazepine. One subject was already being treated for epilepsy with valproic acid at a dosage of 900 ± 92 mg day⁻¹ (92 mg L⁻¹). A dose reduction to 600 mg day⁻¹ (45 mg L⁻¹) unexpectedly resulted in a moderate stabilization of mood and behaviour.

Table 2 Functional domains of unstable mood disorder (*n* = 28)

<i>Domain</i>	<i>Number</i>	<i>Percentage</i>
<i>Mood</i>		
Rapid mood swings	6	21
Mood swings	16	57
Episodic dysphoria	16	57
<i>Anxiety</i>		
Anxieties	7	25
Irritability	13	46
<i>Motor</i>		
Disorganized behaviour	6	21
Hyperactivity	13	46
Stereotypies	10	36
Self-injuries	7	25
Impulsivity	7	25
Aggression	15	54

Table 3 Global improvement versus current illness state at endpoint in subjects treated with valproic acid ($n = 28$)

Severity of illness state	Global improvement				Total
	Very much improved	Much improved	Minimal improvement	No improvement	
Normal:					
number	1				1
percentage	3.6				3.6
Marginal:					
number	8	1			9
percentage	28.6	3.6			32.1
Mild:					
number		7			7
percentage		25.0			25.0
Moderate:					
number		2	2		4
percentage		7.1	7.1		14.3
Severe:					
number				4	4
percentage				14.3	14.3
Very severe:					
number				3	3
percentage				10.7	10.7
Total:					
number	9	10	2	7	28
percentage	32.1	35.7	7.1	25.0	100

At the baseline, responders ($n = 19$) and non-responders ($n = 9$) did not differ with respect to age and the types of symptoms belonging to the three domains. At the endpoint, no differences could be demonstrated between both response groups with regard to either the dosage or plasma concentration of valproic acid. The tapering off of co-medication after having achieved moderate to marked improvement did not influence the clinical response nor the stability of behaviour. Psychotropic co-medication was not related to the degree or nature of the clinical response.

Discussion

In the present exploratory pilot study, the effect of valproic acid was investigated in 28 subjects with ID who were assumed to suffer from unstable mood disorder characterized by long-lasting episodic disturbances in the mood, anxiety and motor domains. Ideally, a time-series analysis is appropriate to assess treatment effects in subjects with fluctuating symptomatology. However, the CGIS has a widespread application in psychiatry and its validity has been established in affective disorders (Leon *et al.* 1993). A clinically relevant and sustained improvement in terms of both behaviour stability and symptom reduction was observed in 68% of the subjects. The treatment effects of valproic acid were noticed at a mean daily dose level and mean plasma concentration of 1343 mg day^{-1} and 63 mg L^{-1} , respectively.

Because no signs of hypomania or major depression were observed, the disorder in these subjects cannot be regarded as belonging to the bipolar spectrum with or without

a rapid cycling course. The mere finding that valproic acid is effective in the majority of the subjects included in the present controlled treatment study does not automatically imply that the unstable mood disorder belongs to the bipolar affective disorders. Thus, the results cannot easily be compared with those obtained by others investigating subjects with ID and bipolar affective disorders (Sovner 1989; Kastner *et al.* 1993; Ruedrich *et al.* 1999). The diagnostic category of atypical or unspecified bipolar disorder is most probably given in many cases (Deltito 1993; Jacobsen 1993; Gross & Huber 1996). The present authors have previously reported an ICD-10 diagnosis of unspecified bipolar affective disorder in 14 subjects described in a study of neuropsychiatric consultations in 70 institutionalized subjects with ID, (Verhoeven & Tuinier 1997).

The unstable mood disorder proposed in the present paper resembles the description of the ICD-10 diagnosis of cyclothymia (F34.0), in which cyclic changes in behaviour and sociability may dominate (WHO 1992), but lacks periods of elation. As elegantly observed by Gualtieri (1991), subjects with developmental disorders frequently show affective symptoms which may be extremely debilitating and may require intensive pharmacological treatment, but which only occasionally meet the diagnostic criteria for a discrete major affective episode. The problematic nosological status of sub-affective syndromes, such as cyclothymia, has been debated in the psychiatric literature for more than a century (Brieger & Marneros 1997).

The relatively low prevalence of subjects with epilepsy in the present study may be related to either a stabilizing effect of anticonvulsants in general or an interference of these compounds with neurobiological stress-regulating mechanisms (Verhoeven *et al.* 1999). The latter holds particularly for valproic acid since this anticonvulsant acts on the hippocampal serotonin 1a receptor that is involved in stress reactivity (Shiah *et al.* 1977).

As reviewed by Guay (1995) and Davis *et al.* (2000), disorders which respond in general to valproic acid share elements of psychopathology such as mood instability, behavioural dyscontrol, anxiety, impulsivity, agitation and hyperarousal. This advocates a dimensional approach with behavioural elements and symptoms which cut across psychiatric diagnoses. Such a perspective is in agreement with the functional psychopathological paradigm advocated for many years by H. M. Van Praag (Van Praag & Leijnse 1965; Van Praag *et al.* 1990). In cases of so-called unstable mood disorder, the relevant functional disturbance is instability, which entails episodic changes in behaviour, mood and anxiety (Verhoeven & Tuinier 2000).

Although it can be argued that the present study has methodological shortcomings, a clear symptom profile, albeit an inter-individually different one, of unstable mood disorder in people with ID could be identified that appears to be responsive to treatment with valproic acid. Given this profile, future studies should include the Aberrant Behavior Checklist (Aman 1985) since its items cover the anxiety and motor domains. However, heterogeneity in genetic aetiology and level of ID, as well as somatic and neurological comorbidity, still warrants a multiple $n = 1$ design.

Acknowledgments

The authors are indebted to the medical and psychological staff of the Vizier/Saamvliet and Kempenhaeghe institutes for developmental disabilities in Gennepe and Heeze, respectively, for their willingness to cooperate and to collect the subject data. We are also grateful to the Foundation Consulententeams for Persons with Intellectual Disabilities

and Severe Challenging Behaviour, Veldhoven, the Netherlands, for its coordinating activities.

Correspondence

Any correspondence should be directed to Professor W. M. A. Verhoeven, Vincent van Gogh Institute for Psychiatry, Stationsweg 46, 5803 AC Venray, the Netherlands.

References

- Akiskal H. S. (1994) Dysthymic and cyclothymic depressions: therapeutic considerations. *Journal of Clinical Psychiatry* **55** (Suppl. 4), 46–52.
- Akiskal H. S. (1996) The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. *Journal of Clinical Psychopharmacology* **16** (Suppl. 1), 4–14.
- Aman M. G. (1985) The Aberrant Behavior Checklist: a behavior rating scale for the assessment of treatment effects. *American Journal of Mental Deficiency* **89**, 485–491.
- Brieger P. & Marneros A. (1997) Dysthymia and cyclothymia: historical origins and contemporary development. *Journal of Affective Disorders* **45**, 117–126.
- Bumke O. (1929) *Lehrbuch der Geisteskrankheiten*. Verlag von J. F. Bergmann, München.
- Davis L. L., Ryan W., Adinoff B. & Petty F. (2000) Comprehensive review of the psychiatric uses of valproate. *Journal of Clinical Psychopharmacology* **20** (Suppl. 1), 1–17.
- Deltito J. A. (1993) The effect of valproate on bipolar spectrum temperamental disorders. *Journal of Clinical Psychiatry* **54**, 300–304.
- Duncan A. G. (1936) Mental deficiency and manic-depressive insanity. *Journal of Mental Science* **82**, 635–647.
- Einfeld S. L. & Aman M. (1995) Issues in the taxonomy of psychopathology in mental retardation. *Journal of Autism and Developmental Disorders* **25**, 143–167.
- Gross G. & Huber G. (1996) Depressive or mood disorders in operationalized classification systems and the affective psychoses (manic-depressive illness, cyclothymia) of the traditional psychiatry. A critical review. *Neurology, Psychiatry and Brain Research* **4**, 149–158.
- Gualtieri C. T. (1991) *Neuropsychiatry and Behavioural Pharmacology*. Springer-Verlag, Berlin.
- Guay D. R. P. (1995) The emerging role of valproate in bipolar disorder and other psychiatric disorders. *Pharmacotherapy* **15**, 631–647.
- Guy W. (1976) *Early Clinical Drug Evaluation (ECDEU) Assessment Manual*. National Institute on Mental Health, Rockville, MD.
- Jacobsen F. M. (1993) Low-dose valproate: a new treatment for cyclothymia, mild rapid cycling disorders, and premenstual syndrome. *Journal of Clinical Psychiatry* **54**, 229–235.
- Kastner T., Finesmith R. & Walsh K. (1993) Long-term administration of valproic acid in the treatment of affective symptoms in people with mental retardation. *Journal of Clinical Psychopharmacology* **13**, 448–451.
- Leon A. C., Shear M. K., Klerman G. L., Portera L., Rosenbaum J. F. & Goldenberg I. (1993) A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. *Journal of Clinical Psychopharmacology* **13**, 327–331.
- Matson J. L., Coe D. A., Gardner W. I. & Sovner R. (1991) A factor analytic study of diagnostic assessment for the severely handicapped scale. *Journal of Nervous and Mental Disease* **179**, 553–557.
- Meins W. (1994) Psychische Störungen bei geistiger Behinderung – Prävalenz und psychopathologische Besonderheiten. *Zeitschrift für Klinische Psychologie und Psychopathologie und Psychotherapie* **42**, 274–285.
- Ruedrich S. (1993) Bipolar mood disorders in persons with mental retardation: assessment and diagnosis. In: *Mental Health Aspects of Mental Retardation* (eds R. J. Fletcher & A. Dosen), pp. 111–130. Lexington Books, Free Press McMillan Inc., New York, NY.
- Ruedrich S., Swales T. P., Fossaceca C., Toliver J. & Rutkowski A. (1999) Effect of divalproex sodium on aggression and self-injurious behaviour in adults with intellectual disability: a retrospective review. *Journal of Intellectual Disability Research* **43**, 105–111.

- Shiah I. S., Yatham L. N., Lam R. W. & Zis A. P. (1977) Effects of divalproex sodium on 5-HT_{1a} receptor function in healthy human males: hypothermic, hormonal, and behavioural responses to ipsapirone. *Neuropsychopharmacology* **17**, 382–390.
- Sollier P. (1901) *Psychologie de l'idiot et de l'imbécile*. Ancienne Librairie Germer Bailliere et Cie., Paris.
- Sovner R. (1989) The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders. *Journal of Clinical Psychiatry* **50** (Suppl. 3), 40–43.
- Van Praag H. M., Asnis G. M., Kahn R. S., Brown S. L., Korn M. & Friedman J. L. (1990) Nosological tunnel vision in biological psychiatry. A plea for a functional psychopathology. *Annals of the New York Academy of Sciences* **600**, 501–510.
- Van Praag H. M. & Leijnse B. (1965) Neubewertung des Syndroms. Skizze einer funktionellen Pathologie. *Psychiatria, Neurologia, Neurochirurgia* **8**, 50–66.
- Vanstraelen M. & Tyrer S. P. (1999) Rapid cycling bipolar affective disorder in people with intellectual disability: a systematic review. *Journal of Intellectual Disability Research* **43**, 349–359.
- Verhoeven W. M. A. & Tuinier S. (1997) Neuropsychiatric consultation in mentally retarded patients: a clinical report. *European Psychiatry* **12**, 242–248.
- Verhoeven W. M. A. & Tuinier S. (1999) The psychopharmacology of challenging behaviours in developmental disabilities. In: *Psychiatric and Behavioural Disorders in Developmental Disabilities and Mental Retardation* (ed. N. Bouras), pp. 295–316. Cambridge University Press, Cambridge.
- Verhoeven W. M. A. & Tuinier S. (2001) Two steps forward, one step back: paradigmatic changes in psychiatry. *Journal of Neural Transmission*, in press.
- Verhoeven W. M. A., Tuinier S., Van den Berg Y. W. M. M., et al. (1999) Stress and self-injurious behaviour: hormonal and serotonergic parameters in mentally retarded subjects. *Pharmacopsychiatry* **32**, 13–20.
- World Health Organization (WHO) (1992) *ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization, Geneva.