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BIPOLAR DISORDER – FROM ENDOPHENOTYPES TO TREATMENT

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SUMMARY

Introduction: *There are a lot of unresolved issues associated with the classification, diagnosis, clinical management and understanding of the underlying pathogenic mechanisms of bipolar affective disorder.*

Aim: *To search for discrete endophenotypes in BAD.*

Subjects and methods: *We studied various bipolar I and II and recurrent depression patient samples and healthy controls using descriptive data, self and clinician-rated scales for neurological and psychopathological symptoms, neurocognitive instruments, and inventories for temperamental and characterological features. We also looked into the efficacy, tolerability and cost/benefit ratio of sodium valproate in the treatment of acute mania.*

Results: *BAD patients display deficits in the domains of memory, selective attention, working memory and psychomotor speed. Sensory, motor and complex neurological soft signs can be considered part and parcel of the symptomatology of BAD. The evidence linking hyperthymic temperament to the bipolar spectrum is not supported, while cyclothymia seems to be a marker of vulnerability to affective psychopathology. In contrast to others, we found significantly lower self-transcendence in BAD patients compared to controls. Early age of onset, abrupt onset, lability of mood and energy with late-day brightening and activation, discriminate bipolar from unipolar depression. Sodium valproate (especially if started intravenously) is a highly efficacious, cost-effective treatment approach for acute mania.*

Conclusion: *The discovery of BAD endophenotypes can enhance early diagnosis, prevent errors in treatment and help elucidate the genetic vulnerability for this grave disease.*

Key words: *bipolar disorder – endophenotypes – cognition - neurologic soft signs – temperament - bipolar depression - sodium valproate*

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INTRODUCTION

Bipolar affective disorder (BAD) is a common, persistent, and severe mental illness. Its defining features bind together numerous psychopathological domains (elation, depression, anxiety, psychosis, impulsivity, aggression, suicidality, addiction, disorders of sleep and activity), as well as different mental and medical diseases. Thus, it stands right in the core of psychiatry as we know and practice it.

There are a lot of difficulties and unresolved issues associated with the study and management of BAD. Many bipolar patients remain misdiagnosed for extended periods of time (Ghaemi et al. 1999). The predisposition to BAD is expressed through a whole spectrum of phenotypes with progressive brain damage over time. The course is undulant, erratic, often resulting in a chaotic life trajectory, and a plethora of comorbid somatic and psychopathological conditions may be present. The definition of the disorder relies heavily on cross-sectional phenomena. BAD presents the most peculiar and illogical exceptions in the categorical approach of the DSM IV-TR (APA 2000): the borders between BAD I and II are defined by the level of impairment while the borders between BAD I and schizoaffective disorder are defined by the precise timing of psychotic symptoms inside or outside of affective episodes, and by their "congruence" to mood. Response to treatment (most often in the form of "staged polypharmacy") is staggeringly heterogeneous with huge inter-individual differences and worrisome intra-individual fluctuations over time. There is a wide and often unbridgeable gap between symptomatic and functional recovery.

Kraepelin was probably right when he stated: "The real, the deeper cause of manic-depressive illness is to be sought in a permanent morbid state which must also continue to exist in the intervals between the attacks" (Kraepelin 1921); in other words, in BAD there remains an incompletely elucidated underlying disease with mania and depression simply representing its extremes (or even complications).

AIMS

Our group endeavored to tease out that which is permanent in the constantly changeable and to demonstrate how clinical observations and neuropsychological studies can provide clues about the underlying basic disease mechanisms.

ENDOPHENOTYPES

At the beginning of our comprehensive study of BAD we asked ourselves if the endophenotype concept could help (Hranov 2009). Endophenotypes are measurable components along the pathophysiological pathway between etiology and psychopathology (Gottesman & Gould 2003). An endophenotypic marker

should be associated with the illness in the population under study, be heritable and co-segregate with the disease in the affected families, be independent from the current clinical condition, and be found in unaffected close relatives in rates higher than those in the general population (Glahn et al. 2004). The construction of endophenotypes of BAD could be instrumental to refining the diagnostic criteria, describing predictors of symptomatic variants, creating a possibility of an exact early prognosis for patients and close relatives alike, and preventing erroneous treatment. In this manner we can select and study homogenous subgroups and eventually direct research to individual vulnerability/ susceptibility genes (Gottesman & Shields 1967, Gottesman & Gould 2003). There already are some encouraging examples: A. Both susceptibility to BAD and susceptibility to autoimmune thyroiditis co-segregate at least partially in some families (Vonk et al. 2007); B. There is a statistically significant linkage of BAD to a chromosome 18q locus in the families of patients with BAD+panic disorder compared to the families of "pure" BAD (MacKinnon et al. 1998); C. Neuronal hyperexcitability due to mutations of ion channels can produce a combination of migraine+BAD in some families (Oedegaard et al. 2010).

Behavioural dimensions found in numerous mental disorders, medical conditions and healthy individuals could lead us to definable endophenotypes. The search for endophenotypes in BAD seems most warranted in cognition, discrete impairments of brain functions, neuronal excitability (expressed as temperament variability, hyperactivation, impulsivity, anxiety, paroxysmal symptoms), as well as in distinct combinations with comorbid conditions.

Cognition

Cognitive impairment is a good candidate for an endophenotype, being that it is associated with the illness, present in mania and depression in at least 1/3 of the patients, state-independent, persistent and stable in euthymia, familial and heritable (Leboyer et al. 1998, Ferrier et al. 1999, Martinez-Aran et al. 2004, Clark et al. 2002, Christensen et al. 2006).

We studied 12 bipolar patients in acute manic episode (equal number of males and females; mean age 42.4±10.7 years) and 12 controls (83.3% females; mean age 28.3±9.7 years) using a neurocognitive battery consisting of Raven's progressive matrices, Stroop colour and word test, TMT-A & B, Bourdon's attention test, verbal fluency test (letters K, C, M in Cyrillic), digit-symbol substitution test, digit recall test, and a 10 words learning test (Pandova & Hranov, unpublished). Even with such a small number of patients and controls, there were significant inter-group differences in test performance. Bipolar patients displayed significant memory dysfunction encompassing encoding, storage and retrieval ($p<0.005$; $p<0.039$; $p<0.032$, respectively). Patients performed significantly worse than controls on all measurable indices of the Stroop test ($p<0.000$), suggesting serious impairment of selective attention and inhibitory control. Working memory and psychomotor speed were also impaired in bipolar patients in comparison with healthy controls ($p<0.044$; $p<0.000$, resp.). Our results are in agreement with the most frequently reported results in scientific literature (Bearden et al. 2001, Osuji & Cullum 2005, Sachs et al. 2007, Swann et al. 2009) and differ widely from the cognitive deficits (and, ipso facto, from the neuroanatomical underpinnings) reported for OCD and for Parkinson's disease by another member of our research group (Fineberg et al. 2010, Hranov 2012).

Neurological soft signs (NSS)

NSS are minimal, non-localising, objectively measurable abnormalities indicating damage of the cortical-subcortical connections suggesting specific deficits and not simply a general brain dysfunction (Gupta et al. 1995). According to the results of a factor analysis, neurological signs are covered by five factors: 'motor coordination', 'sensory integration', 'sequencing of complex motor tasks', 'right/left and spatial orientation' and 'hard signs' (Schröder et al. 1991). These factors are related to dysfunctions of particular brain regions which are identical to the regions associated with the specific cognitive deficits in BAD and schizophrenia. Thus, NSS in BAD correlate with the deficits in executive functions and attention in all stages of the illness (Thompson et al. 2005, Goswami et al. 2006).

We studied 20 bipolar patients in manic, mixed or depressive episodes (40% males; mean age 41.75±11.30 years) with no history of CNS organic disorders, abuse/dependence or uncontrolled medical conditions in comparison to 20 matched healthy controls (45% males, mean age 40.35±15.11 years) (Stoyanova & Hranov 2013) using HAM-D, YMRS, and the Heidelberg Scale for NSS (Schröeder et al. 1991). The mean number of NSS was 8.9±4.12 for the bipolar group and 4.7±2.67 for the controls. There were significant inter-group differences for the sensory, motor, and complex NSS ($p<0.016$; $p<0.006$; $p<0.0003$, respectively), while we did not find any statistical difference between bipolar patients and controls for orientation and neurological hard signs. Moreover, there were no clinically detectable tics in the bipolar group which was in striking difference to the 72.1% incidence of tics found in a group of 104 OCD patients (Hranov & Fineberg 2010), supporting the notion that tics are a discrete endophenotype of OCD (Hranov & Hranov 2008). The number of NSS did not correlate with the severity of the depressive/manic symptoms which was also in sharp contrast to the correlation between number/severity of tics and severity of OCD symptoms (Hranov & Fineberg 2010).

Temperament

This is a basic predisposition to a level of activity, affective tone, or mood, and their intensity, reactivity and variability. Temperament has a more stable, constitutional, biological basis than personality. By definition, the hyperthymic temperament is free of depressive features, and the depressive temperament does not contain any hyperthymic component. Cyclothymic and irritable temperaments present with a successive and simultaneous mixture of hyperthymic and depressive features. These temperaments are not independent of each other: the pairs of depressive and anxious temperament, and cyclothymic and irritable temperament are closely interrelated and also show high correlation to all other scales. Hyperthymic temperament is the only one that appears independent of all others (Akiskal et al. 2005, Rozsa et al. 2008).

According to many investigators, affective temperaments reflect the core characteristics of manic-depressive illness and in fact represent the milder manifestations of the bipolar spectrum (e.g. Akiskal & Pinto 1999, Akiskal & Akiskal 2005). Especially, hyperthymia is considered to be the most correlated with emotional and behavioral problems (Signoretta et al. 2005) and to often precede and underlie bipolar II disorder (Perugi & Akiskal 2002). Others (e.g. Hantouche et al. 1998) believe that cyclothymia is a special constitution; a pathological temperament which is neither madness, nor normality (”antechambre de la folie”) (Kahn 1909).

We studied 53 patients (22.6% males; mean age 50.7 years) with a major depressive episode (MDE) (Marinova & Hranov 2013) of at least moderate severity using the TEMPS-A. It is a 110-item self-assessment scale with depressive, cyclothymic, hyperthymic, irritable and anxious subscales rooted in an evolutionary biologic perspective and framed in the language of affectivity (Akiskal & Akiskal 2005). Its clinical validity has been supported on a genetic basis (Gonda et al. 2006). The patients were divided into two well-defined and demographically matched groups: A. Recurrent major depression (RMD) of at least 5 years duration, with no previous (hypo)manic/mixed episodes and no first degree relatives with bipolar spectrum disorders (n=18), and B. Major depressive episode (MDE) in well-established BAD (N=35; 17 BAD I and 18 BAD II). Cyclothymic and irritable temperaments were equally distributed among the unipolar and bipolar groups (0.56 : 0.58, n.s. and 0.31 : 0.33, n.s., resp.). Hyperthymic temperament was slightly less common in BAD (0.33 : 0.37, n.s.) while anxious temperament was much more common in RMD (0.77 : 0.62, $p<0.004$). No significant correlation between age and temperament was found.

We also applied the TEMPS-A to 205 clinically healthy students (59% females; mean age: 22.45+3.8) and to 66 hospitalized patients (76% females; mean age: 47.71+11.2) with DSM-IV diagnosed major depressive episode (Marinova 2013). Four subgroups of depressive patients were analyzed: 1) first depressive episode (1MDE) patients (n=14); 2) RMD patients as defined above (n=18); 3) BAD I patients (n=16) with at least one prior manic episode; 4) BAD II patients (n=18). All patient groups except the 1MDE group displayed significantly lower hyperthymic temperament scores compared to the controls ($p<0.05$). There was no statistical difference between the MDD and BAD subgroups. For all patient groups, hyperthymic temperament scores correlated negatively with suicidal ideation ($r=-.332$, $p=0.006$). These results are similar to the findings of other researchers (Karam et al. 2010, Vazquez et al. 2008, Vazques et al. 2010) and do not support the inclusion of hyperthymic temperament in the bipolar spectrum (Akiskal & Pinto 1999, Perugi & Akiskal 2002).

Character/Personality

Personality unites the unique aspects of an individual, especially those which are most distinctive or most likely to be noticed by others in social interactions. An individual’s personality develops early, is stable, and has a strong heritable component. The relationship between mood disorders and personality has been of longstanding interest to clinicians. Personality traits and disorders have a strong influence on the course and outcome of mental disorders and may affect the response to certain treatment modalities or influence what treatments patients receive (Mulder 2002). Throughout the years, personality has been alternatively conceived to be a predisposition, an expression or a modifier of affective illness and also to be altered by affective illness (Goodwin & Jamison 2007).

Together with temperament, character forms the core of human personality. It comprises the particular cognitive and interpersonal style, defenses, expectations, and patterns of response. Character is weakly heritable, and is also shaped by environmental and sociocultural learning experiences.

Cloninger's Temperament and Character Inventory (TCI) is based on a seven-dimensional psychobiological model comprises three character traits: self-transcendence, cooperativeness, and self-directedness, as well as four temperamental traits: persistence, reward dependence, novelty seeking, and harm avoidance (Cloninger et al. 1993, Cloninger et al. 1994). Higher self-transcendence (ST) scores in bipolar patients have been reported in uncontrolled samples of bipolar patients (Osher et al. 1996, Kamel et al. 2009), in comparison with unaffected controls (Loftus et al. 2008) and patients with major depressive disorder (Nowakowska et al. 2005, Harley et al. 2011). Some authors suggest that high ST may be specific to BAP (Harley et al. 2011). As ST is heritable, genes that affect it may be relevant for vulnerability to BAD. It is very intriguing that high ST has been associated with polymorphisms of the glycogen synthase kinase 3beta (GSK3β) gene

(Serretti et al. 2008) as that enzyme may have a pivotal role in the pathophysiology of BAD (Hranov 2011).

We are inclined to agree that a distinction of the bipolar disorders according to temperament and character could be more useful than the actual bipolar I – bipolar II distinction (Del Debbio 2010). This is why we applied the TCI to 20 bipolar patients in manic, mixed or depressive episodes (40% males; mean age 41.75±11.30 years) with no history of CNS organic disorders, abuse/dependence or uncontrolled medical conditions, in comparison to 20 matched healthy controls (45% males, mean age 40.35±15.11 years) (Stoyanova & Hranov, unpublished). Out of the seven factors there was a robust intergroup statistical difference only for self-transcendence (patients : controls = 11.55±6.48 : 17.75±6.9, $p<0.01$). Thus, our results are in opposition to the already quoted data of others, which might be explained most plausibly by the presence of both affective poles in the sample.

Clinical indices

We have been mostly interested in the early distinction between unipolar and bipolar depression and in the importance of anxiety as a potential endophenotype of BAD.

A. Unipolar and bipolar depression

Kraepelin's manic-depressive psychosis included alternating mania and melancholia, all cases of mania, and seemingly all depressions (Kraepelin 1921). In effect, Kraepelin viewed all affective disorders as manic-depressive. The unipolar-bipolar distinction was incorporated much later in the DSM-III (APA 1980) following the seminal independent work of Angst and Perris (Angst 1966, Perris 1966). Bipolar disorder presents initially with a depressive episode in 35% to 60% of patients (Kinkelin 1954, Ghaemi et al. 1999) making accurate early diagnosis very difficult. There are currently no accepted specific diagnostic criteria for bipolar depression for either research or clinical purposes. The delay in proper diagnosis of BAD is a major challenge to contemporary psychiatry and has a grave impact on treatment outcome and on long-term prognosis, especially considering the fact that cross-cultural studies have found switch rates among initially depressed patients to be as high as nearly 40% in follow-ups from 3 to 13 years duration (Rao et al. 1977, Akiskal et al. 1995).

To identify potential historical and clinical markers of bipolarity allowing early recognition of bipolar affective spectrum disorders, we studied 53 patients (41 females and 12 males; mean age 50.7 years) with at least moderately severe major depression (Marinova & Hranov 2013). Symptomatology was assessed by the clinician-rated Bipolar Inventory of Symptoms Scale (BISS) (Bowden et al. 2007) which measures not only depression and mania but also anxiety, irritability, and psychosis. The patients were distributed into two well-defined groups: 1) RMD as defined above (n=18); 2) MDE in patients with well-established BAD diagnosis (n=35; 17 BDI and 18 BDII). The age of onset for the first MDE was 4.7 years earlier in BAD than in RMD (n.s.). 40% of the bipolar and 17% of the unipolar depressive patients reported a sudden, abrupt onset of the first depressive episode (p=0.015). 57% of the bipolar and only 11% of the recurrent depressive patients reported afternoon/evening brightening of mood (p=0.005). 42.85% of the BAD and 16.67% of RMD patients had attempted suicide (p=0.057). BAD patients suffered more severe impairments of concentration (p=0.010), more mood lability, and experienced much more frequent evening activation (p=0.033). 57% of BAD patients displayed at least one persistent manic symptom during the index depressive episode. Our results are in accordance with many clinical and psychometric studies as well as multivariate analyses that focus attention on rapid shifts in mood and energy (e.g. Ahearn & Carrol 1996, Mitchell et al. 2008). It is good to remember that Kraepelin gave more weight to a dimensional continuum of "pressure of activity" which he thought to be "the fundamental manifestation" of the disease. (Kraepelin 1913; pp 28-29). We can only agree that "focusing on behaviours, rather than mood, is of paramount importance in the early diagnosis of bipolar affective disorder" (Bowden 2005). One possible explanation of such findings could be that the underlying dysregulation of the central behaviour activation systems is more severe in bipolar disorder (Cuellar et al. 2005).

B. Anxiety in BAD

Anxiety disorders comprise the commonest psychiatric co-morbidity of the bipolar spectrum (Karam et al. 2010). Moreover, anxiety has achieved the status of a separate specifier of BAD in the DSM-V (APA 2013). We studied 31 patients (24 females and 7 males; mean age 48.3 years): 6 suffering from RMD and 25 having a bipolar MDE (12 BAD I and 13 BAD II) (Hranov & Marinova 2012). When measured by the Spielberger's Trait-State Anxiety Inventory (STAI), no difference was found either for state (RMD 57.39 vs BAD 58.11, p=0.714) or for trait anxiety (56.19 : 56.91, p=0.619). 50% of RMD and 16% of BAD patients (p=0.078) had a history of generalized anxiety disorder, panic disorder, social phobia or OCD. BAD patients with comorbid anxiety disorders displayed the highest mean group STAI score.

Therapeutic issues

We assigned 19 acutely manic patients (10 males and 9 females; mean age 40.4 years; 17 BAD I and 2 BAD II) to a stepwise treatment with sodium valproate (SV) for a period of 21 days (Hranov et al. 1998a). Efficacy was measured by the Bech-Rafaelssen Mania Scale (BRMS) and CGI, and tolerability by UKU. Evaluations were done on days 0, 3, 5, 7, 14 and 21.

LOCF-type analysis was used. During the first three days SV was applied intravenously b.i.d. in a fixed dose of 1200 mg/day. If by that time a reduction of the BRMS score by at least 30% was not achieved the i.v. application went on for two more days. After this initial period the patients continued on 20 mg/kg/day SV orally. 15.8% of the patients dropped out of the study before its completion (2 for lack of efficacy and 1 because of side effects). The total LOCF BRMS score was progressively reduced by 26.2% on Day 3, 36.9% on Day 5, 41.3% on Day 7, 43.2% on Day 14, and 43.2% on Day 21 (49.8% for the protocol completers). The LOCF CGI-S was reduced by 48.7% with 68.4% of the patients having a score of 2 ("borderline") or less. 78.9% were considered at least to have marked improvement. The three most frequent adverse effects were skin rashes, nausea/vomiting and orthostatic hypotension, each affecting 10.5% of the patients. Being mild and transient, these events did not necessitate discontinuation of treatment or dose reduction. One of the patients (with a history of head trauma) developed severe sedation (sopor) and had to be withdrawn from the study on Day 10, recovering in two days without any sequelae. 63.2% of the patients did not report any adverse effects. Additional BDZ were used during the first five days by 31.5% of the patients due to sleep disturbances and/or motor restlessness. A small matched sample of 17 patients on a conventional neuroleptic regimen was used as a comparative group. CGI showed a highly significant difference in favor of SV on Day 7 ($p<0.1$), Day 14 ($p<0.01$) and Day 21 ($p<0.001$) with a 4-fold lower group severity score and 2.7-fold greater improvement score at the end of the study.

This was the first report in the literature of intravenous administration of SV in acute manic episode (Lennkh & Simhandl 2000) advancing a rapid-acting and highly effective treatment approach for these hard-to-treat patients

We performed a head-to-head comparison of lithium (Li) and SV in an international, randomized, open-label, parallel-group equivalence study of 268 patients with BAD I (Bowden et al. 2010). The SV starting dose was 20 mg/kg/day and Li was given as 800 mg/day carbonate salt. SV and Li showed comparable efficacy and tolerability in the treatment of acute mania over 12 weeks. The mean reduction of the Young Mania Rating Scale (YMRS) score was 15.8±5.3 for the Li group and 17.3±9.4 for the SV group. Response rates were 72.6% vs 79.5%, and remission rates were 58.5% vs 71.9%, respectively. No inter-group differences were observed in the median time to treatment response (21 days), or in the reduction of the CGI-BD and MADRS scores. Mild and transient adverse events were reported by 42.8% of patients on Li and by 41.5% on SV.

A pharmacoeconomical vignette

The costs of stepwise SV IV/PO was compared to "usual care" (UC = antipsychotics+benzodiazepines) for the treatment of acute manic episode (27 patients aged 41.3 years on SV and 15 patients aged 43.9 years on UC, resp.) (Hranov et al. 1998b). The total cost of the stepwise SV treatment amounted to only 53.4% of the UC cost for a 21-day hospital treatment. All UC patients and 40.7% of the SV patients reported adverse events ($p<0.001$). 48.1% of the SV group did not need any additional medication. 80% of the UC group and 14.8% of the SV group were rehospitalised during the next 12 months ($p<0.001$). There was a very robust difference in the cost/effectiveness and cost/benefits ratios in favour of the stepwise SV treatment approach.

Note: Statistical analysis in all studies was conducted by using the SPSS-17.0 package (ANOVA, Mann-Whitney test, chi-square test, t-test, Fisher exact test, Pearson correlation, etc.).

Limitations

The samples in most of our studies comprised a small number of patients and controls, and some are uncontrolled. The designs are observational, cross-sectional, and retrospective, mainly due to a complete lack of funding since the beginning of our research.

Future steps

This is a comprehensive effort in progress. In addition to our ongoing studies, we have begun investigating impulsivity in BAD, sleep disorders, medical comorbidity in BAD, and have begun developing the concept of "mixity".

CONCLUSIONS

The preliminary results of our 15-year long studies in the field of BAD allow the following tentative assumptions:

- The search for discrete endophenotypes in BAD is a fruitful and promising path leading to a more comprehensive and profound understanding of the underlying neurobiology.
- The most conspicuous cognitive deficits in BAD are found in the domains of memory, selective attention, working memory and psychomotor speed.
- Sensory, motor and complex neurological soft signs can be considered part and parcel of the symptomatology of BAD.
- The evidence linking hyperthymic temperament to the bipolar spectrum is not supported while cyclothymia seems to be a vulnerability marker for affective psychopathology.
- The notion that high self-transcendence may be a specific feature of BAD is not supported (without wading into the state/trait controversy).
- Certain clinical features allow early recognition of bipolar depression with a reasonable reliability (e.g. early age of onset, abrupt onset, mood and energy lability with late-day brightening and activation).

- Sodium valproate (especially if started as a fixed-dose intravenous infusion of 1200 mg/day for the first 3–5 days) is a highly efficacious, cost-effective treatment approach for acute mania.

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