

Volume 11, Issue 3, Year 2011

**ROMANIAN JOURNAL OF
PSYCHOPHARMACOLOGY**

**Editura Medicală Universitară Craiova
2011**

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ISSN 1582-7674

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TREATING MAJOR DEPRESSION IN HOSPITALIZED PATIENTS WITH PARKINSON'S DISEASE: A 20-YEARS RETROSPECTIVE CHART REVIEW

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Abstract

Background: Few studies have systematically evaluated the impact of antidepressant treatment on depression in Parkinson's disease (PD). One such recent NIH sponsored study shows that nortriptyline produced significantly more responders than did paroxetine CR. This raises questions about the relative efficacy of selective serotonin reuptake inhibitors (SSRIs) in PD depression.

Methods: A retrospective analysis of the files of depressed patients with PD hospitalized between 1989-2009. Disease stage and outcome were evaluated using the Hoehn and Yahr scale for PD and the CGIC and CGI were used for depression outcome.

Results: Of 680 charts reviewed, 30 patients (14 men, 16 women) were diagnosed with PD and co-morbid depression. Mean age was 75 ± 5 years. PD duration was 12.7 ± 13 months, with a median PD stage (Hoehn & Yahr) of 3.0. Median depression duration was 49.5 ± 10 months. Median CGI at baseline was 5 (range: 4-7). Twenty six patients were treated with DOPA, 4 with dopamine agonists and 4 with amantadine; twelve patients were previously exposed to SSRIs. During hospitalization 7 patients received SSRIs, 18 selective noradrenergic reuptake inhibitors (SNRIs), two with other agents (one with trazodone and one with buspirone) and 3 had electroconvulsive treatment (ECT). In 12 patients second generation antipsychotics (SGA) augmentation was employed. Mean depression remission was attained at 1.5 months. At discharge the mean CGIC was 2.5 ± 0.6 (median: 2).

Conclusion: Improvement was achieved in 93% of PD depressed inpatients and better response was achieved when a combination of SNRIs and SGA or ECT were used.

Key words: major depressive disorder, Parkinson's disease, therapy.

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Introduction

Among the general psychiatric patient population depressive symptoms may appear as a unique mood disorder or part of schizophrenia, personality disorders, drug abuse and others; among the elderly depressive symptoms may result from several additional age related conditions and particularly dementia and Parkinson's disease. In some patients antidepressant use may antedate the onset of motor symptoms (Alonso et al., 2009). The prevalence of depression is 31% for all PD patients (James et al., 2001). Depression in PD more often presents as minor depression (22%) or dysthymia (13%) rather than major depression (17%). Of the 4 inpatient studies reviewed and included in this study one indicates a prevalence of 21.7% for major depression and 3 others a prevalence of 54.3% for clinically relevant depressive symptoms. Suicide has been very rarely reported. (Reijnders et al., 2008). Depression coincides often with anxiety and panic attacks during motor "offs". The parkinsonian patients have been described as having a more introvert, anacoustic personality, being punctual, accurate and inflexible. During the past 20 years surgery for PD has become an alternate solution for patients non-responsive to drug treatment. This treatment alternative has also shown complications in the affective domain. A survey including 5311 PD patients undergoing DBS found that the rate of completed suicide was 0.45% (24/5311) and attempted suicide was 0.90% (48/5311). Observed suicide rates in the first postoperative year (263/100,000/year) (0.26%) were higher than the lowest and the highest expected age-, gender- and country-adjusted World Health Organization suicide rates (Standardized Mortality Ratio for suicide: SMR 12.63-15.64; $P < 0.001$) (Voon et al., 2008).

With regard to the neurochemical background, the level of 5-hydroxyindoleacetic acid (a major metabolite of serotonin) is reduced in the cerebrospinal fluid suggesting that serotonergic dysfunction occurs in the brain of PD patients (Yamamoto, 2001).

Given the large number of PD patients who suffer from depression it is surprising that few randomized controlled clinical trials have been undertaken to evaluate the efficacy and tolerance of pharmaceutical treatment. Tricyclic antidepressants (TCA) have undergone double-blind placebo controlled testing (Andersen et al., 1980), but more clinicians prefer to use selective serotonin reuptake inhibitors (SSRIs) in treating depression associated with PD based on their experience with fewer side effects in elderly patients (Burn, 2002). An older survey published in 1997 of 49 investigators from the Parkinson's Study Group or PSG (this group has experience with over 23,000 PD patients) found that 51% of physicians use SSRIs first when implementing drug therapy. This is contrasted with the 41% who use TCAs and the 8% who use "other" drugs (Richard and Kurlan, 1997).

Wermuth et al., 1998 reported negative results of a randomized controlled trial (RCT) with citalopram in PD depression. Leentjens et al., 2003 decided to terminate early a trial of sertraline versus placebo after failing to recruit more than 12 patients after 30 months, during which both arms show the same rates of improvement, reaching the conclusion that " results indicate that in our patient sample most of the benefit obtained with the active drug might derive from a placebo effect".

A controlled trial of antidepressants in patients with Parkinson disease and depression conducted by Menza M et al. found that response rates favored nortriptyline ($p = 0.024$): nortriptyline 53%, paroxetine CR 11%, placebo 24%. Nortriptyline was also superior to placebo in many of the secondary outcomes; including sleep, anxiety, and social functioning (Menza et al., 2009). The same authors also provided the first controlled trial showing the impact of treatment of depression on quality of life (QoL) and disability in PD. Their findings suggest that successfully treating depression in PD leads to important, sustained improvements in these outcomes (QoL, relapse, tolerability, safety, and the impact of depression treatment on PD physical functioning), also that patients who improve on antidepressants are less likely to relapse than are patients who initially improve on placebo (Menza et al., 2009). The use of antidepressants seems indeed to have positive effects on depression in PD, but so does also the agonist pramipexole that had a beneficial effect on mood and motivational symptoms in PD patients who did not have major depressive disorder (Leentjens et al., 2009). Another earlier RCT focusing on pramipexole mentions that UPDRS part I focusing on mentation and behavior improved noteworthy (Wermuth, 1998).

The data regarding PD inpatients with comorbid major depression is scarce, as more depressed PD patients suffer of minor depression or dysthymia and are thus treated in outpatient settings. This prompted us to assess depression treatment in elderly PD inpatients admitted during the past twenty years to our psychiatric center.

Methods

A retrospective analysis of computerized medical charts of elderly depressed inpatients treated in the psycho-geriatric department at our center during the period Jan 1989 to March 2009 was undertaken. The study was approved by the local IRB. The Abarbanel Mental Health Center (AMHC) is a university affiliated tertiary care center servicing an urban catchment area of Tel Aviv –Jaffa and southern suburbs with approximately 850,000 people, of which 14% are elderly (65 years and above). Depressed patients are hospitalized in AMHC based upon the following criteria: (I) psychotic depression (II) suicidal thoughts or suicide attempt (III) long standing non-reactive depression that caused significant functional impairment and/or extreme self-neglect.

PD inpatients with depressive symptoms that were hospitalized in the psycho-geriatric department of AMHC during the above mentioned period were screened according to the following criteria: (a) a diagnosis of PD based upon the UK Parkinson's Disease Society Brain Bank requiring the presence of two out of the four cardinal symptoms of: bradykinesia, rigidity, resting tremor and postural instability (b) anti-parkinsonian medication was instituted and doses were escalated according to response or when side effects appeared. In case anti depressant medication did not lead to remission of depression ECT was given and in some cases second generation antipsychotics (SGA) were added

as augmentation therapy. (c) major depressive episode (diagnosed following a structured clinical interview according to DSM-IV criteria for depression [SCID-D]) (American Psychiatric Association, 1994), (d) treated with at least one antidepressant during the current episode and (e) severity of current episode warranting inpatient treatment. We recorded from each chart: duration of PD, duration of depression, time to remission, medication used during previous depressive episodes and during the current episode, medical co-morbidities and current medical treatment.

Outcome measures:

The Clinical Global Impression scale (CGI-S) (Guy, 1976) is a three-item scale used to assess treatment response in psychiatric patients. Severity is rated on an eight-point scale (0=not assessed, 1=normal, not at all ill, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill to 7=amongst the most extremely ill); Improvement on a seven-point scale (1=very much improved, 2=moderately improved, 3=mild improvement, 4=no change, 5=mild worsening, 6=moderate worsening to 7=very much worse); The Clinical Global Impression of change (CGIC) was defined as the primary outcome in the present study. The Hoehn and Yahr scale was used for motor assessment (Hoehn and Yahr, 1967).

Results

During the study period of 680 elderly inpatient admissions to our center, 30 fulfilled the inclusion criteria, showing a prevalence rate of 4.4% of hospitalized PD patients with major depression. These included 16 female (%) and 14 male (%), mean age 75 ± 5 years (range: 65-86), PD median duration: 12.7 ± 13 months and median PD stage (Hoehn & Yahr) was 3; mean depressive episode duration 49.5 ± 10 months. Physical comorbidity was common in the group with the leading comorbid conditions being: hypertension – 7 patients, diabetes – 5 patients and dyslipidemia – 3 patients, ischemic heart disease – 2 and gastro-intestinal tract disorders – 2.

Prior to hospitalization 12 patients had been treated with an SSRI with no clinically meaningful response, despite optimal therapeutic doses. In 6 of these patients SGA augmentation was attempted prior to admission. Additional psychiatric medication included sedatives in 9 and mood stabilizers in 2. As for antiparkinsonian medication; 26 patients were treated with DOPA, 4 were also receiving dopa agonists (ropinirole), and 4 patients received amantadine.

All PD patients were diagnosed with co-morbid major depression. In 8 patients cognitive impairment was also diagnosed.

Patients were treated by antidepressants as follows: 7 with an SSRI and 18 with a SNRI, two with other agents (one with trazodone and one with buspirone). SGA augmentation was employed in 12 patients. Three patients received ECT in addition to antidepressant medications when response to medication only was considered inadequate (see Table).

Table: Patient demographic characteristics and treatment in the different CGIC categories

CGIC	1	2	3	4	6
Number of patients	1	15	12	1	1
Gender (M/F)	F	8/7	6/6	F	F
Age	65	75.8±5.4	74.5±4.3	78	82
Duration of PD since diagnosis (months)	24	15.5	8.2	30	2
Hoehn and Yahr stage of PD	3	3	3	3	4
Depression Duration (weeks)	8	62	84	36	24
Time to remission (weeks)	4	5.2	6.4	-	-
Treatment employed	venlafaxine, olanzapine followed by ECT	6 - SSRIs 11 - SNRIs 4 - SGAs 2 - ECT	6 - SNARs 6 - SGAs 1 - Buspirone	Paroxetine, risperidone	Trazodone

Legend: ECT=electroconvulsive treatment, SSRIs = serotonin reuptake inhibitors, SNARs = serotonin noradrenalin reuptake inhibitors, SGAs = second generation antipsychotics

At beginning of hospitalization median CGI-S score was 5.0 (range: 4-7). At end of hospitalization the CGIC mean score was: 2.5 ± 0.6 with a median of 2.0 as half of the patients scored 2 (much improved), 12 patients scored 3 (mild improvement) and one patient scored 1 (very much improved). Response rates (as measured by improvement scores of 1-3 on the CGIC) were very favorable, in the range of 93%. Mean time to depression remission for the group was 1.5 months.

Discussion

The aim of this study was to retrospectively evaluate the treatment outcome of depression in hospitalized elderly PD patients. The issue of prevalence of depression in PD depends on the type of population analyzed and its source (general population, inpatient or outpatient setting, nursing home, etc.), also whether the diagnosis was made according to interview or depression scales. The prevalence rate of 4.4% for our elderly hospitalized PD patients with major depression was lower than previously described (21.7%) (Costa et al., 2006). This might be due to the fact that we describe a PD inpatient population all being diagnosed by interview with major depression. The use of depression scales like the Geriatric Depression scale or the Hamilton depression scale might have yielded a higher prevalence but might have also included PD patients with dysthymia or minor depression. These patients, who could not be managed elsewhere, had to be confined to the psychogeriatric ward of our psychiatric center and represent a very unique group of the most seriously ill PD patients.

Our study shows that most PD patients with depression are classically treated with SSRIs as previously reported by Burn, 2002 (7). Almost a third of PD-depressed patients are treated with SSRIs even after hospital admission, according to our study. Response rates were very favorable (in the range of 93%)

and attained during a relatively short time of psychiatric hospitalization (6 weeks). Baseline depressive symptoms were unrelated to motor functioning. In a different recent study treatment response was associated with significant improvements in the core mood, anxiety, insomnia, and somatic symptoms seen in depressed PD patients. Residual symptoms, such as sadness and loss of interest, persisted in treatment responders in a milder form than was initially present (Dobkin et al., 2010).

This study has several limitations: its' retrospective design, using an interview for diagnosis of depression without the aid of depression scales and a relatively small sample size. However, the unique sample of inpatients suffering from PD and severe co-morbid depression may add to the limited data available in this population.

Conclusion

In our study best responses seem to be reached when a combination of SNRI and SGA were employed as already shown (Baune et al., 2007) or an SNRI and ECT was used, but the small number of patients treated with ECT precludes generalization of our findings.

We urge the medical community to produce more studies of treatment of depression in PD, as these are urgently needed in order to generate guidelines for the treatment of depression in PD.

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CURRENT PHARMACOLOGICAL OPTIONS IN THE THERAPY OF BORDERLINE PERSONALITY DISORDER

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Abstract

Borderline personality disorder is a very complex psychiatric nosological model. It is enrooted in-between the biological and temperamental vulnerability and the diversity of comorbid conditions belonging to both Axis I and II of multi-axial diagnosis. In this context, any therapeutic strategy necessarily becomes multidimensional and flexible, through constant association of psychotropic medication and psychotherapy. Recent studies dedicated to borderline personality disorders along with personal therapeutic experience with borderline patients are pleading for therapeutic programs associating the last generation antipsychotics with mood stabilizers.

Key words: *borderline, multidimensional, therapeutic approach*

The borderline personality disorder (BPD) represents an extremely complex model of psychiatric illness, not just a personality disorder. Its structure and dynamics are conditioned, above all, biologically, but also socially and culturally. (Bateman and Fonagy, 2007)

The term borderline has a multitude of meanings (Simonsen, 1994), but has first of all connotations of severity which overshadow any attempt at a clinical description. The association or alternation between the pathological temperament and character types and a diversity of pathological symptoms belonging to the diagnostic Axis I, give borderline personality disorders an evolving clinical polymorphism that has unique attributes. Within it, behaviors belonging to all three clusters of personality disorders can coexist or alternate, especially those of the paranoid, schizoid, histrionic, antisocial and dependent personality types. In this context, a major consequence seems to be a difficulty to diagnose them, due also to the intermittent nature of borderline states which can affect an individual's destiny.

We must underline that the prevalence of the borderline personality in the general population is between 0.2% and 1.8% in the US, and 0.7% in Scandinavia (Schwartz et al., 1990; Torgersen et al., 2001). However, the prevalence is 10% in outpatient psychiatric clinics, 20% in psychiatric

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hospitals, and 80% in forensic psychiatric units, together with paranoid and antisocial personality disorders (Rutter and Greeven, 2000; Dolan and Coid, 1993).

Borderline patients are frequent users of psychiatric services, as well as social services. This is due to the borderline behavior, which constantly integrates contrasting feelings, impulsivity, conscience disturbances, self-mutilations, and suicidal attempts (Zanarini et al., 2004; Paris and Zweig-Frank, 2001). The latter are quite frequent, being described in 59% out of 250 borderline patients belonging to a group studied by Grilo et al., in 2001.

In the same context, the manipulative behavior of the borderline patient often succeeds in captivating and mobilizing those around them - including the therapeutic staff - in order to receive supportive intervention, even though its efficiency remains limited due to the structural instability of the disorder.

The above-mentioned elements endorse BPD with a particular gravity. This gravity can also be evaluated according to the number of criteria a patient meets – out of the 9 criteria of DSM IV, as well as the criteria used in diagnosing other personality disorders (PD), and which the patient partially meets. It can be compared to a mixed or polymorphic personality type, and belongs, according to Tyrer & Stein (1993), to the severe PDs or may be considered an extensive PD (Oldham and Skodol, 2000; Westen and Shedler 2000).

In a dimensional sense, BPD can be considered an extreme expression of neuroticism from the Big Five model (Costa and Mc.Crae, 1992), and it has a very low level of spiritual opening from the Big Seven model (Cloninger et al., 1993) corresponding to an instability of one's self-image and affect. This instability has a net effect on one's self-determination, relationship with fellow human beings, and the capacity for self-transcendence. According to Millon et al. (1996), BPD can also be seen as an association of the extreme manifestations of paranoid, histrionic, and passive-aggressive personality disorders.

Neuroticism, BPD, bipolar affective disorder, and impulse control disorders are related in that the latter represent maladaptive variations of BPD which thus becomes a variant of the Axis I diagnostic disorders.

Particular attention is to be given to a series of clinical and evolutionary peculiarities of BPD which constantly complicate diagnosis. Borderline type traits such as disorders of self-perception, states of depersonalization, extreme or paradoxical affective and motivational mood swings, are integrated into the psychotic prodromal manifestations. The sharpening of these personality traits could trigger a first episode of affective psychosis, but also a schizophrenic one (Nirestean et al., 2005). The same traits can contribute to the longer duration of the untreated psychosis in young people, since they can be masked by age-characteristic psychological dominants, and can later bring about a turn toward schizophrenia of certain psycho-pathological symptoms which were initially affective.

Also from a diagnostic perspective, if we approach separately the BPD disorders of Axis I and II, they almost constantly associate co-morbid conditions like depression, anxiety, impulse-control disorder, dissociative and paranoid episodes, substance abuse, and obsessive-compulsive manifestations, and can condition one-another with post-traumatic stress disorder (Lazarescu and Nirestean, 2007).

The coexistence of the symptoms of Axis I diagnostic syndromes which are often preponderant, with borderline- type maladaptive behaviors based on low self-esteem and self-control, always complicate diagnosis, and inherently, therapy. The latter must combine psychotherapeutic and pharmacological techniques which address both the socio-cultural and the biological conditionings of BPD.

Any therapeutic strategy must consequently take into account the gravity of BPD manifestations which always have a tortuous or unpredictable evolution, alternately dominated as it is by contradictory psycho-behavioral symptoms. Likewise, there is also the conviction of the patient, as a result of projection, that the uncertainty and uneasiness are attributes of the therapist, whom he still feels attracted toward. Borderline patients also have a well-known and well-practiced capacity of exploring the cognitive and affective content of their interlocutors, in search of self-protection. Therapeutic intervention is negatively impacted by the quasi-permanent association between a state of generalized disconnection and a transitory hyper-availability.

The main argument for the psychopharmacological treatment of BPD derives from its extremely complex biological conditioning. It is sustained by PET studies and neuromediators measurements that confirm a diminished activity of the orbital frontal area corresponding to the deficiencies in self-image, the smaller volume of the hypo-campus, amygdala, as well as of the limbic system. They consecutively affect the capacity to integrate images, and the visual and verbal memory that loosen the ties between past and present, the quality of one's biographical experiences as well as that of one's affective responses. Likewise, the diminished level of the central serotonin explains the impulsive manifestations, while the dysfunction of the dopaminergic system facilitates pathological cognitions (Zanarini, 2005).

Though the first treatment recommended for any personality disorder is psycho-therapeutic intervention (Soloff, 2005). Because of the peculiarities of its pathogenesis and of its clinical evolution, BPT is an illness that always requires psychotropic medication. This medication stabilizes psycho-behavioral manifestations and facilitates the psycho-social therapeutic intervention.

The studies of Pennes (1954), Vilkin (1964), Klein (1967), Montgomery and Montgomery (1982), and Soloff (1989) described the medicinal therapies in BPD and confirm the utility - relativized by a series of characterial and biological variables – of amital, amphetamines, diazepam, tranlylcipromine, and haloperidol in reducing borderline-type behaviors. They drew attention to certain secondary effects like the lack of inhibition, hypotension and weight gain.

The affective nucleus of BPD, - and within it - the depressive dimension which triggers a significant suicidal potential, imposes the need for anti-depressive medication. Nowadays, starting from the premise of a deficient tolerance of try-cyclic and IMAO anti-depressive medication, the SSRI medication is being used on a large scale. The studies of Norden (1989), Cornelius et al. (1990), Markovitz and Wagner (1999) and Rinne et al. (2002) show the usefulness of SSRI in the treatment of depressive behaviors associated or not with anxiety, but they cannot differentiate their anti-depressive action from that against negative affectivity which is seen as a dimension of BPD. Jick et al. (2004) comment about the rising suicidal potential of a group of patients treated with amitryptiline, fluoxetine, paroxetine, and deothepine, though non-discernable in the patients who were only give fluoxetine. Sexual dysfunction and akathisia as secondary phenomena are not statistically or qualitatively significant.

The modern anti-depressants that are used – fluoxetine, sertraline, venlafaxine, as well as citalopram (Reist et al. 2003) can be used alternatively. They are useful in diminishing irritability and verbal impulsivity as well as in the general functional level of the BPD patients (Coccaro and Kavoussi, 1997). Psychotic and psychotic-like episodes associated with BPD can benefit from neuroleptic medication. Classical antipsychotics cannot replace the latest generation ones, which are much better tolerated and whose pharmacokinetic profile is more complex.

In this context, the efficiency of clozapine has been confirmed by the studies of Frankenburg & Zanarini (1993) Benedetti et al. (1998), and Parker (2002). In spite of the well-known secondary effects, in less than half the patients under study medication was not interrupted. Clozapine, given in a medium dosage between 44 and 253 mg. /day, significantly reduced psychotic episodes and both shortened the duration of hospitalization and the role-playing of the patients under study.

Olanzapine proves to be a last-generation neuroleptic, and has efficiency comparable to that of clozapine in treating cognitive, affective, impulsive, and hypersensitive interpersonal behaviors of borderline patients (Schultz et al., 1999, Zanarini & Frankenburg, 2001). Rocca et al. (2002) also describe the useful effect of risperidone has in the treatment of psychotic and depressive episodes, as well as the social behavior of borderline patients, but Schultz et al. (1999) consider it to be only comparable to a placebo effect. The secondary metabolic effects were insignificant, nevertheless the glycemic and blood lipids levels needs to be monitored.

In borderline patients, the affective instability, the impulsivity but also the depressive symptoms can be treated with mood stabilizers. The studies of Gardner & Cowdry (1986) confirmed the use of carbamazepine in controlling impulsiveness in women, but the well-known secondary effects of the medication have limited ulterior (follow-up) experiments.

Stein (1995), Wilcox (1995), Frankenburg and Zanarini (2002) confirm the role of sodium valproate in diminishing the anxiety, impulsivity, dysphoric crises, and hypersensitivity of borderline patients. The same results are obtained by Simeon, Baker, Chaplin, Braun & Hollander (2007).

Huband, Ferriter, Nathan and Jones (2010) make a meta-analysis of 14 studies which include 672 patients with recurrent aggressive manifestations with sodium valproate, carbamazepine, oxcarbazepine, and fenitoin. They confirmed the relative utility of these medications, the sodium valproate and fenitoin having an effect mostly in treating the impulsivity of PD patients. The usefulness of lithium-based medications has not been confirmed in the case of borderline patients (Links et al., 1990).

Depressive symptoms and aggressiveness also responded to an Omega 3 fatty acid, the ethyl eicosapentaenoic acid, in women with BPD (Zanarini & Frankenburg, 2003).

The use of benzodiazepine in BPD is not advised due to its addictive potential, and the rise of impulsivity. Clonazepam, if used in half dosage for a longer period of time, is recommended for patients with co-morbid anxiety disorders (Chouinard, 1987).

The psychopharmacological treatment of BPD remains a permanent challenge due to the complexity of the psycho-pathological manifestations and the vulnerability of character which make difficult the patient-therapist relationship and the patients' adherence to treatment.

The latter can be improved by the associated presence of certain depressive symptoms, and by the fear of abandonment which stabilize the hypersensitivity specific to borderline patients.

The BPD patients' commitment to following therapeutic advice is problematic because of the subordination-hostility syndrome which is sustained by the structural deficit of the Ego, and the alternate projections on the therapist of the feelings of safety and fear. For BP the internal representation of the medication- the imagined model of it- is more important than the medication itself. That is why they intermittently 'choose' the medication or the dosage to be used at a certain time, thus in congruence with their personal momentary needs.

There are no specific medications for BPD, but in general one can confirm the effectiveness –for the majority of the psycho-behavioral manifestations- of small doses of last-generation antipsychotics, of SSRI, and of valproic acid salts. The extreme gravity of BPD is also proven by the fact that clinical praxis constantly imposes the use of psychotropic medications, and the introduction of a new medication requires through analysis. The short term hospitalizations and the availability of outpatient centers always make compliance to therapy easier.

Independent of the efforts of the therapists, BPDs have more or less the ability, though problematic, to direct any therapeutic strategy that aims at diminishing the severity and variety of the behaviors which push them away, and simultaneously get them so much closer to the extremes of the human condition.

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THE CONTROVERSY OF PSYCHOPHARMACOLOGICAL TREATMENT VS. PSYCHIATRIC DISEASES

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Abstract

Science, in its evolution, postulates that every assertion should be subjected to denial in order to continually correct it until nothing can be denied anymore. This happens ideally. In fact, once assumed, a scientific theory routinely marks the thinking of generations until the discrepancy between positive affirmations and those which deny the up-to-date scientific theory becomes bothersome. It is when the adjustments begin. In the present paper we briefly reviewed the existing contradictions at this time concerning the psycho-pharmacological treatment of mental illnesses.

Key words: *psychiatric illness, psycho-pharmacology, controversy*

Introduction

According to the dictionary definition, controversy means “a contradictory discussion about something” (Breban, 1987). In our case the controversy lies in the notion of psychiatric disease itself. New classifications have replaced the term disease with disturbance, which is not the same thing. If we care about significance shades, the disease implies an independent situation outside the normal one, while the disturbance, as a general notion, implies a transitory phase of reality. The disease implies a medical status of psychic diseases while disturbances do not imply a medical status of the same realities.

It has become historically obvious that the fate of psychic patients could not be altered until the medical model of psychic diseases appeared. It is the only model which offered viable therapeutic solutions to most psychic diseases. It is true, however, that this model does not cover the entire psychopathological reality and that this one creates a gradual transition to instances of psychic normality, yet this truth does not change the situation, it cannot cancel the medical model of the psychic disease. It merely attaches a pathological aspect whose interdisciplinarity is yet to be cleared out.

The controversy implies uncertainty about something. If you are not sure whether it is a disease, then what do you treat? Or why do you treat? Not calling something a disease, yet treating it as a disease is a

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stupid contradiction. This shadow of a doubt is transferred from diagnosis level to treatment level. We cannot extend to the controversy of all the therapy models present in psychiatric practice that is why we are going to refer to medicine treatment. Here the controversies have two levels: a) the ethical-social one and b) the punctual technical one of the biological intervention.

The purpose of the present paper is to synoptically collect controversy regarding psychopharmaceutical therapy.

Methods

The method consists of systematically approaching the issues in discussion with logical deduction and as outlined in specialized texts.

Results and discussion

Ethical-social controversies

Given the “striking difference between the psychiatric medical treatment and care and that of other medical specializations” (Chadwick, 2004), there are two problems which pose controversies: stigma and autonomy.

It has been proven that stigma alone can maintain a state of illness, or, by non-compliance it can enhance relapse. Our discussion comes down to prodromal psychotic cases, even those with first episode. It is certain at present that not every prodromal state or first episode will evolve into a constituted psychosis, say schizophrenia. “Not every first psychotic episode develops into schizophrenia” says Mc.Gorry (2003). Then, if “frontal cortical atrophy can be primary or secondary to antipsychotic medication” (Marinescu, 2010), how argued is the decision of applying antipsychotic treatment to such cases? If in their evolution the cases become schizophrenics, the treatment is benefic, if they don't, then it is harmful. But not knowing what their future is, which is the good line of action? In this case stigma is also accompanied by dying cell effect of an inexpedient treatment. Is avoiding the risk of schizophrenia worth the risk of cortical atrophy? If we are indeed avoiding schizophrenia as a possible course. The problem is still open.

As far the problem of autonomy is concerned, it is obvious that you cannot give antipsychotic treatment unless you diagnose psychosis. Once you diagnose psychosis, the person concerned is automatically considered to be partial or totally unable to decide. So, a series of restrictions are going to be imposed on that person. We return to prodrom and first episode. Who and after how long will cancel the diagnosis claimed by antipsychotic therapy? I believe that here we should get official permission to administer antipsychotics in different clinical conditions and the therapeutic guides should contain such specifications. The problem is not only ethical, but also juridical. So, another problem to be solved.

Punctual technical level controversies

As far the action of psychotics is concerned, we have an explicatory model which is unanimously acknowledged (Spiegel, 2005; Stahl, 2005; Stahl, 1999). This receptor model has created a “revolution” in psycho pharmacy by explaining every psychic disease by the affection of neurotransmission at receptor level. According to the model, every psychic disease has a specific profile of neurotransmission affection. How is it possible then that the same molecule of antipsychotic to be therapeutically efficient in schizophrenia with positive symptoms, in schizophrenia with negative symptoms, in bipolar depression, in maniacal episodes, in borderline, in some cases of food disorders, even in some cases with atypical depressive episodes from the atypical depressive disturbance (Cornutiu, 2007)? don't these evidences cancel the pretence of specificity of the receptor model?

This means that the explicative receptor model has worn out and that it must be updated or changed. It is not advisable therefore that our explanations should not exclusively approach clinical evidence.

A consequence of this limited knowledge is the delay with which we assessed the therapeutic latency on disease and medication (Cornutiu, 2007). We already know that we owe the phenomenon to the neuroplasticity which precedes the receptor effect, that an accumulation of BDNF and messenger DNA is produced but we do not fully understand the phenomenon (Duman, 2004). We do not know if this therapeutic latency could be correlated with the prognosis and with the length of necessary treatment, an area in which we have been groping for too long.

Actually, in what the length of treatment is concerned, we have a number of empirically established guidelines: two years after the first psychotic episode, five years after the second one, nine to twelve months after a depressive episode, two to four years for TOC, or authors and even guides avoid to offer guidelines (Andreasen, 2001; Maxen, 1995; APA, 2004). They avoid because there are no rigorous studies in this area. This fact seriously affects our authority as specialists.

Conclusion

We have enumerated a series of the most notorious controversies in the psychopharmacologic treatment in order to draw attention at the risk of mythologizing our present knowledge and our everyday therapeutic practices. Routine predisposes to transforming the knowledge at a certain moment into rigid opinions, and then into firm and unconditional beliefs. It is desirable to think clearly.

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THE EVALUATION OF MOOD SYMPTOMS IN BIPOLAR DISORDER: RATING SCALES AND THEIR PRACTICAL UTILITY

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Abstract

Bipolar disorder represents one of the greatest challenges in current psychiatry regarding diagnostic reliability and the outline of the intensity of episodes, and also concerning longitudinal evolution and treatment efficacy. In this sense, the use of scales for screening and evaluating mood symptoms has become more and more popular. Prior to the administration of any scale, a semi-structured interview for an accurate diagnosis should be applied.

The objective of the current study is a critical description of the most cited scales for depression and mania, with an emphasis on their structure, psychometric qualities and utility.

An exhaustive description of the five most cited Medline scales for depression and mania (authors, self/hetero-administration scales, items, investigated domains, application time, validation studies, psychometric properties) is followed by a brief mention of other scales. Critics of the unilateral use of specific scales argue that most of these scales score symptoms rather following a categorical model, being at risk of missing subsyndromal signs, which rather respond to a dimensional model.

Hundreds of psychometric scales, more or less validated in various geographic areas, are used today in order to study depressive, manic or mixed symptoms of bipolar disorder. However, among this huge variety of psychometric tools, there are several generally recognized and widely used scales, which represent standards for the validation of other scales.

Key words: *clinical scales, bipolar disorder, depression, mania.*

Introduction

As early as 1896, Kraepelin emphasized the need for the comparative testing of mentally ill subjects and healthy people. However, only in the past 60 years has testing become a routine procedure in mental health practice and research, being required particularly by the introduction of psychotropic drugs, which can only be evaluated by assessing the severity of the symptom in time. Today, the concept of "evidence-based medicine" has become the predominant clinical framework, promoting the use of clinical guides and rating scales.

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Although the life prevalence of the disease spectrum is high, 20-70% of the cases are underdiagnosed or misdiagnosed. The correct diagnosis is more than a decade late, particularly in bipolar disorder type II (Miller et al., 2010). Ideally, a structured/semi-structured interview should precede diagnosis, in order to eliminate the collection of incomplete data (Suppes and Dennehy, 2005): Schedule for Affective Disorders and Schizophrenia (SADS), Diagnostic Interview Schedule (DIS), the Structured Clinical Interview for the DSM-IV (SCID).

The rating scales used in psychiatry are divided into 3 main categories: observational, hetero-evaluation and self-evaluation scales. Depending on the aim, rating scales are multidimensional (diagnostic, evaluating the functional status, severity of symptoms, adverse effects) and focused on a specific syndrome (evaluating depression, mania, psychotic symptoms, etc.).

Methods

Using the frequency of citation in Medline database as a differential criterion, we have classified and critically analyzed the most used scales for the evaluation of affective symptoms in bipolar disorder with emphasis on their structure, psychometric characteristics and utility depending on the purpose.

Results

Depression rating scales

The ***Hamilton Depression Rating Scale (HDRS)***, the most widely used depression rating scale, was introduced by Max Hamilton in 1960 in order to assess the severity of depression in already diagnosed patients. HDRS is a hetero-evaluation scale that requires 20-30 minutes for administration. Today, it is mainly used in psychopharmacological studies, as well as for population screening, positive depression diagnosis, the monitoring of the evolution of the disease or as a standard scale for validation compared to other depression rating scales. There are several versions of the scale: with 6, 17, 21 and 24 items, the most used being the 17-item variant. The items are assessed on a Likert scale from 0 to 4 or from 0 to 2. A score of 7-17 is estimated to indicate mild depression, a score of 18-28, moderate depression, and a score higher than 28, severe depression. Although still considered by many authors as a reference scale, it has been criticized for its multidimensionality and low sensitivity (Bech, 2006, Demyttenaere and De Fruyt, 2003) and particularly, for including too many items for somatic symptoms, its application being questionable in the case of elderly patients with somatic disorders (in these cases, somatic symptoms cannot be considered as indicators of depression). On the other hand, another limitation of the scale is the fact that it does not assess atypical depression symptoms (hypersomnia, hyperphagia). Based on the Hamilton scale, two structured interview versions were introduced: *Structured Interview Guide for the HDRS (SIGH-D)* and *A structured interview version of the Hamilton Depression Rating Scale (SI-HDRS)*.

The **Montgomery-Åsberg Depression Rating Scale (MADRS)**, introduced in 1979 by Marie Åsberg and Stuart Montgomery, is an observational scale including 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, slowness, failure to feel, pessimistic thoughts, suicidal thoughts), scored from 0 to 6. Depressive symptomatology is usually evaluated over the past 3-7 days and the scores indicate: 0-6 = no depression; 7-19 = mild depression; 20-34 = moderate depression; 35-60 = severe depression. A score lower or equal to 9 means remission (Zimmerman et al., 2004). Compared to HDRS, MADRS is shorter and more rapid to administer (5-10 minutes), being focused on the psychological symptoms of depression. MADRS is mainly used for the evaluation of response to treatment, having good reliability and validity. There is a close correlation between HDRS and MADRS (Möller, 2009), which have similar sensitivity in studies for the detection of the efficacy of antidepressive therapy, but some authors recommend MADRS as a more adequate instrument for this purpose (Khan et al., 2002).

Beck's Depression Inventory (BDI) is the most used self-evaluation scale for depression, developed by Aaron T. Beck et al. in 1961. It includes 21 items (subjective sadness, pessimism, sense of failure, lack of satisfaction, sense of guilt, sense of punishment, self-loathing, self-blaming, self-punishment, crying, irritability, social withdrawal, hesitation, altered self-image, work difficulties, sleep disorders, fatigue, loss of appetite, weight loss, somatic concerns, loss of libido), each item being evaluated according to 4 degrees of severity (from 0 = absent to 3 = very severe). It only refers to the current state (the symptoms of the past 2 weeks are considered). It requires 5-10 minutes for completion. The scores range between 0 and 63, indicating: 0-9 = no depression; 10-16 = mild depression; 17-29 = moderate depression; 30-63 = severe depression. BDI is useful for screening, for the monitoring of antidepressive therapy and for objectifying a subjective clinical improvement, with a particular focus on the cognitive and behavioral symptoms of depression. It is considered the gold standard of self-evaluation scales in depression, although it has been criticized for not clearly differentiating between depression and anxiety. HDRS and MADRS rather reflect the effect of antidepressants, while BDI rather reflects the effect of psychotherapy (Demyttenaere, 2003). Its strengths remain the assessment of depression and the comprehensive approach of the cognitive dimension of depression. The current version is BDI-II. There is also a short version with 13 items.

The **Zung Self-Rating Depression Scale (ZUNG-SDS)** – quantifies the severity of depression and includes 20 items scored from 1 to 4, which cover 3 major areas: affective, somatic, psychological. It requires 5 minutes for application and the score obtained means: below 50 = normal score; 51-59 = minimal or mild depression; 60-69 = moderate depression; 70-99 = severe depression. The scale is not adequate for the study of antidepressants, because it has a low sensitivity to change. The correlation with BDI is weak.

The ***Carroll Rating Scale for Depression (CRS)***, introduced in 1981, is an adaptation of the 17-item Hamilton scale, resulting in a self-evaluation scale for depression. It includes 52 items with "yes" or "no" answers and evaluates the symptoms of the past few days. It is less used, although it is well correlated with BDI.

Other scales used for the evaluation of depression include: *Diagnostic Inventory for Depression (DID)*, *Bech-Rafaelsen Melancholia Rating Scale (MES)*, *Inventory of Depressive Symptomatology (IDS)*, *Harvard National Depression Screening Scale (HANDS)*, *Raskin Depression Rating Scale*, *Major Depression Inventory*, *Hospital Anxiety and Depression Scale (HADS)*, *Bipolar Depression Rating Scale (BDRS)*, *Quick Inventory of Depressive Symptomatology (QIDS)*, *Geriatric Depression Scale (GDS)*.

Mania rating scales

The ***Young mania rating scale (YMRS)***, the most widely used, was published in 1978 by Young et al. It is an observational scale used both as a diagnostic instrument and for the measurement of the severity of symptoms and the longitudinal monitoring of therapeutic efficacy. It is applied by experienced clinicians, it requires 15-30 minutes and it assesses the real-time status of the patient. YMRS includes 11 items, 7 of which (elevated mood, increased motor activity, sexual interest, sleep, language and thought disorders, appearance, awareness of the disease) are rated from 0 to 4, while the rest of 4 items (irritability, speech, language and thought content, aggressiveness) are scored from 0 to 8. The final score will be between 0 and 60: 0-12 = remission of symptoms; 13-60 = hypomania/mania. YMRS has obtained good reliability and validity scores. There is also a version for the evaluation of mania in children, which is in fact intended for parents: *P-YMRS*.

The ***Bech-Rafaelsen Mania Scale (BRMS)*** is the most validated scale for the evaluation of mania and was introduced for the monitoring of manic symptoms during treatment. It is a hetero-evaluation scale that requires 15-30 minutes for administration and rates the symptoms over the past 3 days. It includes 11 items (elevated mood, increased verbal activity, increased social contacts, increased motor activity, sleep disorders, social activities, hostility and irritability, increased sexual activity, increased self-esteem, avoidance of ideas, tonality), each rated on a Likert scale from 0 to 4 points, with scores that are interpreted as follows: 15-20 = mild mania; 21-28 = moderate mania; 29-44 = severe mania. The scale can also be used for the evaluation of mixed conditions, when it is applied along with the Bech-Rafaelsen melancholia rating scale (MES). It has a greater validity than Clinical Global Impression in the assessment of therapeutic response (Bech et al., 2001, Bech, 2002).

The ***Clinician-Administered Rating Scale for Mania (CARS-M)***, developed by Altman et al. based on the criteria of *SADS (Schedule for Affective Disorders and Schizophrenia)*, evaluates the symptoms over the past 7 days and requires 15-30 minutes for administration. The scale contains 15

items grouped in 2 subscales: for manic symptoms (10 items) and for psychotic symptoms (5 items). The items are rated from 0 to 5 or from 0 to 4. Information from both the patient and other sources (medical documents, family members) is used. The thresholds for the severity of mania are: 8-15 = mild mania; 16-25 = moderate mania; over 26 = severe mania. CARS-M is mainly used for screening and for evaluating the severity of mania, as well as for psychopharmacological studies (Altman et al., 1994).

The *Altman Self-Rating Mania Scale (ASRMS)*, introduced in 1997, is the best known and most widely used scale for the self-evaluation of mania. It contains 5 sets of questions focusing on the symptoms characteristic of mania: elevated mood, grandeur, decreased need for sleep, speech pressure and psychomotor agitation. It has a 85.5% sensitivity and a 87.3% specificity (Altman et al., 1997), as well as a good sensitivity to change (Altman et al., 2001); it can be used in the longitudinal evaluation of response to treatment.

The *Mood Disorders Questionnaire (MDQ)*, introduced by Hirschfeld et al. (2000), is a self-evaluation questionnaire for the screening of bipolar disorder. It includes 13 items formulated as questions requiring "yes" or "no" answers, only positive answers being scored one point each. The threshold score is 7 points for hypomania. The administration time is 5-10 minutes. The questionnaire has proved to have a low sensitivity in the detection of the bipolar spectrum (Dodd et al., 2009, Kim et al., 2008), particularly in patients with a low awareness of the disorder (Miller et al., 2004); consequently, its use as a screening instrument is limited, being partly tributary to the categorical approach (Phelps and Ghaemi, 2006).

The following scales can be used for the evaluation of mania: *Mania Rating Guide (MRG)*, *Beigel Manic-State Rating Scale (BMSR)*, *Cognition Checklist for Mania—Revised*, *Internal State Scale (ISS)*, *Self-Report Manic Inventory (SRMI)*, *Manic State Rating Scale*, *Checklist of Hypomanic Symptoms*, *Hypomania Interview Guide*, *Observer Rating Scale for Mania*, *Child Mania Rating Scale*.

Other scales for the evaluation of affective symptoms

The *Positive and Negative Affect Schedule (PANAS)*, introduced by Watson and Clark (1988), evaluates positive and negative affect, both as a state and trait. The scale contains 20 items, each scored from 1 to 5. The scale evaluates symptomatology during 7 different time periods: at this moment, today, over the past few days, over the past week, over the past few weeks, over the past year or in general. Studies indicate a good reliability (Watson et al., 1988).

The *Brief Bipolar Disorder Symptom Scale (BDDS)*, introduced by Dennehy (2004), is a 10-item scale for the measurement of the severity of symptomatology, being derived from the *Brief Psychiatric Rating Scale (BPRS)*. It has been designed as a rapid working instrument, when conditions do not allow the application of a more detailed scale. It has good psychometric properties and a good sensitivity to change and it can also be used in psychopharmacological studies (Dennehy et al., 2004).

Other scales for the study of affective symptoms: *Affective Disorders Evaluation (ADE)*, *Bipolar Inventory of Signs and Symptoms Scale (BISS)*, *Bipolar Disorder Questionnaire*, *Bipolar Spectrum Diagnostic Scale (BSDS)*, *Affective Self Rating Scales for Manic, Depressive and Mixed Affective States*, *Bipolar Affective Disorder Dimension Scale (BADDs)*, *Manic-Depressiveness Scale*, *Daily Mood Worksheet*, *Clinical Monitoring Form (CMF)*, *Mood Swings Survey (MSS)*.

Discussion

There are a multitude of scales that can be used in the study of affective symptoms. MADRS and HDRS continue to be the standards for hetero-evaluation, both in clinical studies and for the validation of other scales. In clinical purposes, for evaluating of response to antidepressive therapy, MADRS is preferred to HDRS, being more rapid to administer. HDRS is used rather in clinical studies and for population screening. BDI is the most widely used instrument for the self-evaluation of depression, having the advantage of covering its cognitive and behavioral aspects, therefore BDI is preferred in evaluating response to psychotherapy. Other depression scales have poor psychometric characteristics and limited use.

Mania is an area in which the instruments of psychometric testing have not developed as much as those for the evaluation of depression. YMRS is the most used scale in this respect, both in clinical and research purposes. Some clinicians prefer BRMS for longitudinal monitoring of manic symptoms or for evaluating mixed states (along with the MES). Considering the low awareness of the disorder, the utility of self-evaluation scales in mania is controversial.

Because certain scales refer to symptoms specific for a particular syndrome, allowing to avoid subsyndromal mixtures, the application of scales with a dimensional bipolar spectrum approach, such as BDDS or BSDS, is discussed.

Conclusions

The use of standardized instruments for the study of affective symptoms ensures a greater systematization and accuracy of the clinician's approach, allowing both a transversal and longitudinal evaluation (at different time periods) of the evolution of the affective episode. Scales are essential in psychopharmacological studies and the knowledge of the available variants allows choosing the adequate instrument depending on the purpose.

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DETERMINATION OF SINGLE-STRAND POLYMORPHISMS CONFORMATION (SCC) OF GHR GENE IN CHILDREN WITH IDIOPATHIC SHORT STATURE

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Abstract

The term of idiopathic short stature (ISS) refers to a wide range of shorter children without specific etiology. ISS includes patients with genetic or familial short stature, those with constitutional delay of growth and abnormally shorter children to parents target height without discovered endocrine deficits. The genetic analyses brought an extra dimension in the investigation of this condition, over 60 molecular defects of growth hormone receptor gene (GHR) are identified so far, but their role in determining of growth deficit is uncertain. In current study, a total of 24 children diagnosed with ISS were carried out polymorphism analyses of SCC (single strand conformation) of the GHR, in order to detect possible defects in this gene.

Key words: *idiopathic short stature, GHR gene, GHR polymorphisms*

Introduction

Idiopathic short stature (ISS) is a condition when an individual's height for age, sex and population group, without evidence of systemic, endocrine, nutritional or chromosome abnormalities. In specific models, children with ISS had normal weight at birth and growth hormone sufficient (Rosenfeld RG 2007). It is estimated that approximately 60-80% of all children below -2SD or shorter meet the definition of ISS.

The diagnosis of short stature is determined after other causes of weakness stature are excluded. Many children and adolescents are short (under percentile 3), have slowed growth rate (below 25 percentile) may have delayed skeleton maturation and attenuation jump at puberty, with or without a family history of some or all of these clinical events.

Etiology of slow growth in childhood and frequently, of delayed jump from puberty stature could not be established in most of these children. Perhaps they have subtle impairment of hypothalamic-pituitary-IGF axis (Rosenfeld RG 2005, Rosenfeld RG 2006).

A variety of studies has indicated that over 25% of ISS children were screened for low levels of IGF-1, despite an apparently normal GH secretion. They represent a small percentage of patients

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with primary IGF deficiency (IGFD), due to rare genetic causes, which may include (Buckway CK 2001, Leschek EW 2004, Park P 2005, Rosenfeld RG 2005, Rosenfeld RG 2006):

- Specific heterozygous mutations of the GH-IGF axis
- Polymorphisms in genes known as GH-IGF axis
- Defects involving genes not identified yet
- Combinations of the factors listed above.

Candidate genes that could be responsible for IGFD include: GH1 (Lewis MD 2004), GHR (mild homo and heterozygous) (Savage MO 2006, Savage MO 2007), JAK2, STAT5b (Kofoed EM 2003) and other components of the GH-signaling cascade.

Since 2003, in The United States the children with ISS have been receiving treatment with biosynthetic GH. This decision was based on the results of several studies that showed not only how to improve short-term growth rate (Finkelstein B 2002, Kemp SF 2005, Leschek EW 2004, Wit JM 2005), but also how to achieve adult stature greater than that provided or than that of placebo treated control groups (Finkelstein B 2002, Wit JM 2005).

Methods

We were selected and included in our study a total of 24 children with idiopathic short stature.

The 24 children, aged 4-16 years (11 boys and 13 girls) had a growth delay of more than 2.25 SD below the average height for age and sex, without evidence of systemic endocrine abnormalities or nutrition, as defined ISS (Rosenfeld RG 2007). To appreciate the growth of the average delay for age and sex, the height Z score was calculated using the formula:

The Z score of the actual height = $\frac{\text{real height} - \text{medium height for age and gender}}{\text{SD (standard deviation for age and sex)}}$. Medium height and SD for age and sex were obtained using standard anthropometric tables made by Prader et al. (1988).

Patients in our study were followed for 1 year a treatment with growth hormone obtained by genetic recombination (rhGH) in doses of 0.2mg/kg/week, administered subcutaneously daily.

In 24 children with idiopathic short stature have been carried out on SSC polymorphisms (single strand conformation) of GH receptor gene, in order to detect possible defects in this gene.

DNA samples were extracted from peripheral blood collected on EDTA from all patients of our study. We have practiced the method of DNA isolation from blood with Wizard Genomic DNA kit (for 300µl whole blood).

Amplification (PCR). We used PCR amplification kit called “PCR Core System”. It was designed to enhance any type of amplicons by Taq polymerase using standard type. There were amplified genomic fragments of specific GH receptor gene exons 2, 3, 4, 5, 6, 7, 8 and 9 using intron primers. Also, the codified portion exon 10 was amplified in three overlapping fragments.

Results

After molecular analysis of GH receptor gene polymorphism SCC, mutations in the region that encodes the extracellular domain of the receptor have been identified in 4 of the 24 children from our study (Fig. 1).

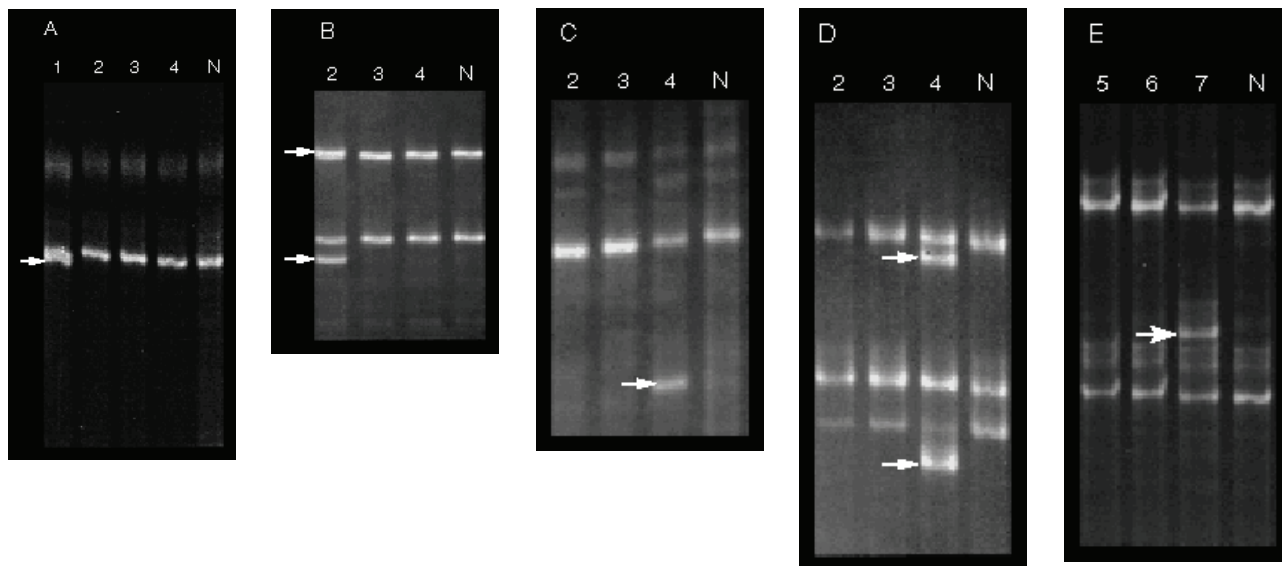


Fig.1. SCC polymorphism analysis of PCR fragments of genomic DNA from 4 children who have mutations in the GH receptor gene. Normal subjects (N) were included in each figure. A - exon 7 in patients 1,2,3 and 4, the excess band with PCR product obtained from patient 1 (arrow) indicates the presence of mutations. B - exon 5 in patients 2, 3 and 4 with excess bands (arrow) in PCR products resulting from patient 2. C, D - C in exon 4 and exon 6 in D in patients 2, 3 and 4. Surplus tapes are observed in the patient 4. E - exon 7 in patients 5, 6 and 7 with an excess bandwidth (arrow) in the sample from the patient 7.

From DNA samples extracted from patient 1, one of the fragments is aberrant genomic PCR (Fig.1). This exon encodes the extracellular domain of GH receptor and did not find any other abnormality affecting this area.

DNA from patient 2 shows an aberrant band in a PCR product of exon 5 (fig.1B). No other mutations were detected at this patient. The most frequent mutation in exon 5 was detected in position 418 it is introduced a stop codon in the place of cysteine in position 122 (Cys 122Stop). This mutant allele is most likely a “null mutation” for not producing a functional protein. Because protein synthesis is stopped at this point, we can not state whether this patient is heterozygous or monozygotic.

The patient 4 has abnormal bands exons 4 and 6. This child has a complex heterozygous mutation in both exon 4 and in exon 6. These two mutations have been identified covering different subcloned regions of exons 4 to 6.

Patient 7, as well as patients 1 and 4 have altered a single allele.

The characteristics of 24 patients with ISS prior to the introduction of treatment with rhGH are shown in Table 1. Patients, whose average age was 9.7 years, had an average delay of growth (the height Z score) of -3.24 DS.

Table 1. Characteristics of patients with ISS prior to treatment

Parameter	Nr.	Average	Dev. Std.	C.V.
Chronological Age	24	9.76	3.19	32.70
Z score of T (DS)	24	-3.24	0.85	-26.35

After a year of treatment with growth hormone, the height Z score reached an average -2.44 DS, and the rate of increase in treatment was 9.5 cm/year (Table 2).

Table 2. Characteristics of patients with ISS after treatment

Parameter	Nr.	Average	Dev. Std.	C.V.
Score Z after treatment (DS)	24	-2.44	0.96	-39.41
Growth rate in treatment (cm)	24	9,50	2.66	27.98

Profile of four patients with mutations in GH receptor gene region encoding the extracellular domain, was as it follows (Table 3):

Table 3. Patients with mutations in the GHR previous treatments

Patient	Sex	Chronological age (years)	Z score	GH*	IGF1
1	M	8	-2.76 DS	0.45	low
2	M	16	-2.64 DS	2.49	normal
4	F	6.11	-3.28 DS	0.15	normal
7	F	5.4	-3.20 DS	2.13	low

* (GH: Normal: 0,5 – 7 ng/ml)

After a year of treatment with rhGH, the Z score of height and growth velocity (cm/year) of the 4 patients was as it follows (Table 4).

Table 4. Patients with mutations in the GHR after treatment

Patient	Z score after treatment	Growth rate in treatment
1	-2.22 DS	8 cm/year
2	-2.27 DS	5 cm/year
4	-2.73 DS	8 cm/year
7	-3.49 DS	4 cm/year

Discussion

Patients with ISS and normal GH secretion were evaluated for abnormalities of GHR gene. Although over 60 molecular defects of the GHR have been described (Savage MO 2006, Savage MO 2007), most patients had normal gene coding regions. Heterozygous mutations of GHR are present at <5% of patients with ISS and their role in determining growth defects is questionable. Exceptions are dominant negative mutations that were seen to affect growth (David A 2007, Metherell LA 2001).

GHR polymorphisms have been also identified in patients with ISS. Two mutations - C422F and P561T - were associated with the ISS, but there is evidence that any of them is functional. It was

shown that there are differences in signaling between wild type and C422F mutation of GHR. P561T was found in 15% of normal population and showed that it is not correlated with height (Leschek EW 2004).

In our group, composed of 24 children with idiopathic short stature, who suffered SSC polymorphism analysis of GHR gene, we identified four mutations in the gene region encoding the extracellular domain of GH receptor (Fig.1).

One of four children with mutations in heterozygous GHR complex had a conformation with abnormal bands exons 4 and 6. This patient had a mutation that reduces the affinity of the GH receptor and another mutation that may affect receptor function other than ligand binding. The other 3 children had a single altered allele. One of these mutations introduces a premature termination codon and the other two cause a single aminoacid substitution in conserved structural domain of the receptor (Fig.1).

Initially rhGH therapy was originally intended only to children with GH deficiency in the recent years the list of diseases that can benefit from this treatment has greatly expanded, the idiopathic short stature being part of them (Bridges N 2005, National Institute for Clinical Excellence 2002).

After a year of treatment with recombinant growth hormone gene, the 24 children in our group with ISS had a mean improvement of height Z score of -3.24 DS from -2.44 SD (Tables 1, 2).

Out of the 4 patients with GHR mutations, three showed a Z score of height improve after treatment and at patient number 7 with age of 5.4 years stature deficit widened from -3.20 DS to - 3.49 DS (Table 3, 4).

Patient number 4 with age of 6.11 years although had a complex heterozygous conformation with abnormal bands exons 4 and 6, the growth rate under treatment was 8 cm/year compared with patients 2 and 7, that showed a single alteration alleles and the growth during therapy was only 5 cm/year and 4 cm/year.

It is hard to know whether poor response obtained to treatment at 3 of the 4 patients with genetic defects is due to abnormalities found or it is the result of the influence of other factors: age, low rhGH dose, genetic factors, etc.

In 2004, there were published results of a study conducted on two cohorts of children short, without growth hormone deficiency: children with idiopathic short stature and children born small for gestational age (SGA). The children received recombinant growth hormone gene and the response to therapy was studied in genotype of growth hormone receptor gene, namely full-length (GHRfl) and exon 3-deleted (GHRd3). Results showed that at children with isoforma GHRd3 growth was 1.7 to 2 times faster than at those who had isoforma GHRfl. This observation suggests that exon 3 polymorphism of GHR is important in growth hormone pharmacogenetics (Dos Santos C 2004).

In children with ISS, doses of rhGH and/or dose adjustment based on serum IGF-1 levels during therapy can improve growth rate (Cohen P 2007).

As we have seen, the ISS comprises a wide range of patients with different causes of short stature. Some of them have a degree of GH deficiency and response well to rhGH replacement, while others may have GH resistance and are candidates for treatment with recombinant IGF-1 (rhIGF-1). So far, no studies have been reported experience with IGF-1 therapy in patients with ISS. On the other hand, there are many reports on growth therapy with rhGH deficiency (Hintz RL 2005, Leschek EW 2004, Park P 2005, Wit JM 2005) in this population because it has been recently approved.

There are already ongoing studies to assess biomarkers of genomics and proteomics for the assessment and management of small stature and to assess responsiveness to therapy with GH and/or IGF-1. While mutations in genes involved in GH-IGF axis have been identified in patients with various growth disorders, attention began to be focused on polymorphisms affecting the function of these genes and their expression. In future studies, biochemical phenotypes auxological will be used to assess protein and candidate genes that might correlate with primary and secondary IGF deficiency (IGFD) or IGF resistance. In addition, attention should be given to non-IGF-dependent factors, known to act on the epiphyseal growth cartilage: SHOX gene, fibroblast growth factor receptor (FGFR0)-3, C natriuretic peptide receptor (NPR2) and other yet unidentified factors (Olney RC 2006, Rappold G 2007, Vajo Z 2000).

Conclusions

Genetic analysis brought an extra dimension in the investigation of small stature, but still, the nature of the particular mutation is not a predictor of response to specific therapy to promote growth. Identifying a specific genetic mutation is nevertheless of great importance in clarifying the etiology of the defect growth.

RhGH therapy remains an important ally in improving the stature deficit in children with ISS. This was observed in our group of patients whose Z score improved on average from -3.24 SD to -2.44 SD.

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COMORBID MEDICAL CONDITIONS IN BIPOLAR PATIENTS

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Abstract

Introduction: Bipolar disease is rarely presented without co-morbid conditions. Without axis I and II diseases, there can be a great incidence of medical conditions interfering with bipolar disease outcome. Obesity, diabetes, dyslipidemia, cardiovascular diseases, thyroid dysfunctions can be the reasons for which this patients have a high morbidity and mortality.

Purpose: this study aims to evaluate the comorbid medical conditions in bipolar patients.

Material and methods: 193 bipolar patients at our Psychiatric University Hospital and affiliated services were entered in an extensive prospective study between 2007 and 2010 regarding medical and psychiatric co-morbidities. BPD diagnosis was based on current criteria (DSM IV TR, HAMD, YMRS). We investigated further how medical conditions influences the prognosis of diseases and quality of life of patients.

Results: The analysis of these 193 patients showed a prevalence of cardiovascular diseases of 38.34%. A total of 48.70 patients were overweight and 32 patients meet criteria for diabetes. Only 7% of females and 4.5 % of males had thyroid dysfunctions.

Conclusions: The metabolic syndrome, obesity and glucose abnormalities found on bipolar patients represent an important cardiovascular risk. They were both due to the disease itself as well as antipsychotic and antiepileptic drugs use.

Key words: Bipolar disorder, metabolic syndrome, co-morbidity.

Introduction

Despite the traditional intuition of a close link between emotional sphere, stress and cardiac function, the scientific demonstration of this relationship is more often based on subjective judgments or empirical arguments. Depression and heart disease have additive effects, and this combination cause more social dysfunction than each condition taken separately. The impact of depression on the evolution of heart attack is equivalent to that of left ventricular dysfunction and that of history of myocardial ischemia. Mortality rate from cardiovascular disease in bipolar patients versus the general population is 3. Furthermore, when metabolic syndrome is controlled, bipolar disorder itself remains an independent risk factor. In a study that followed 406 patients over 30

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years, cardiovascular mortality was exceeded only by suicide as the cause of death in bipolar patients (1) and was followed by cancer.

The link between stress and atherosclerosis is due to activation of the hypothalamic-pituitary-adrenal axis. Unfortunately we do not have at the moment a biological marker associated with depression that would indicate disruption of this axis through which we can select people at risk.

Increased platelet aggregation and a low degree of systemic inflammation observed in depressed patients may be the mechanism by which bipolar disorder is a significant and independent risk factor for ischemic heart disease. But bipolar patients have more frequently a history of hypertension and more commonly are smokers, things that are also risk factors [8]. Anxiety and affective disorders seem directly related to the main aging marker which is atherosclerosis. The action is exercised either directly on the target of atherosclerosis, vascular endothelium, or indirectly through potentate traditional risk factors (smoking, alcohol, hypertension, dyslipidemia, obesity).

Objective

This study aims to evaluate the co morbid medical conditions in bipolar patients.

Material and methods

193 bipolar patients at our Psychiatric University Hospital and affiliated services were entered in an extensive prospective study between 2007 and 2010 regarding medical and psychiatric co morbidities. BPD diagnosis was based on current criteria (DSM IV TR, HAMD, YMRS). We investigated further how medical conditions like cardiovascular diseases, obesity, thyroid dysfunctions; diabetes influences the prognosis of diseases and quality of life of patients.

Results

Both bipolar and unipolar patients have an increased risk of cardiovascular disease that should be managed in partnership with cardiologists. The analysis of 193 patients admitted in this study showed a prevalence of cardiovascular diseases of 38.34%. The most common diseases were hypertension and myocardic ischemia and were followed by arrhythmias, atherosclerosis, and heart attack (Fig. 1).

Researchers noted an increased risk of fatal coronary heart disease in healthy men with high levels of anxiety, and a 3-6 times higher risk of myocardial ischemia and sudden cardiac death in bipolar patients. In particular SSRI use was associated with low morbidity and mortality from cardiovascular disease (12).

Most drugs used to treat bipolar disease are both associated with weight gain and with the appearance of other components of metabolic syndrome like insulin resistance and dyslipidemia (Table 1).

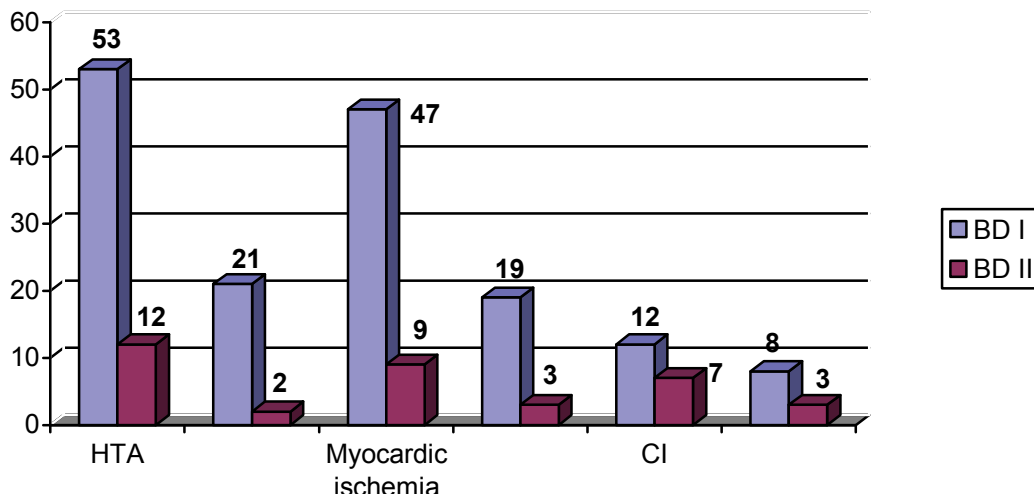


Fig. 1. Cardiovascular diseases in patients with bipolar disease

Table 1. Distribution of patients according to body weight

The degree of obesity	BMI	TAB I	TAB II
Underweight	<18.5	2	0
Normal weight	18.5 - 25	28	21
Overweight	25 - 30	26	6
Gr. I obesity	30 - 35	59	5
Gr. II obesity	35 - 40	6	0
Gr. III obesity	Over 40	3	0

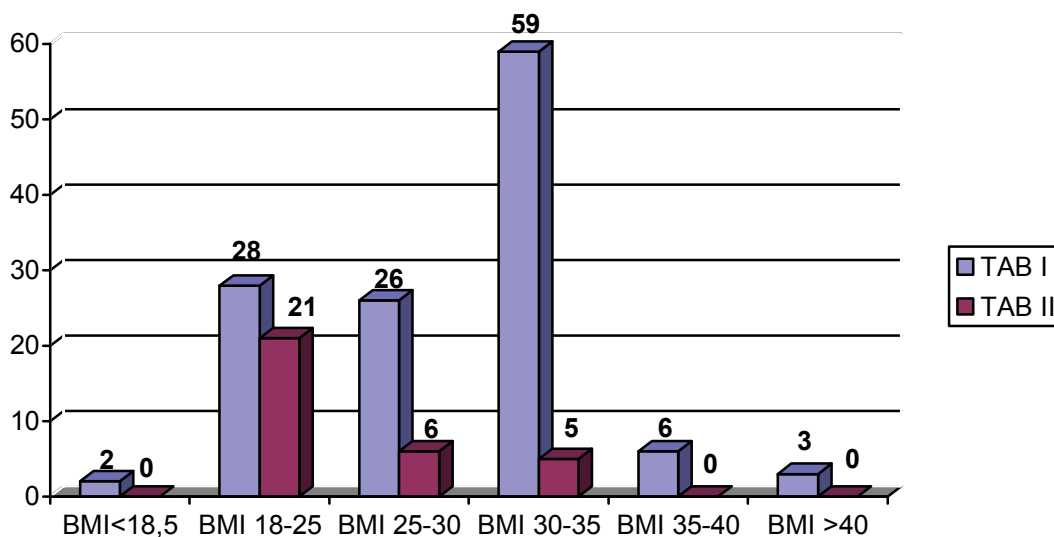


Fig. 2. Distribution of bipolar patients depending on body weight

In our study most patients had a BMI of 30-35 indicating type I obesity. Obesity, dyslipidemia, hyperprolactinemia are sedation and side effects related to antipsychotic agents use. Olanzapine and clozapine were the most commonly used antipsychotics in manic episodes and they were highly associated with metabolic side effects. But it would be noticed that an increased number of depressive episodes was associated with increased risk of obesity.

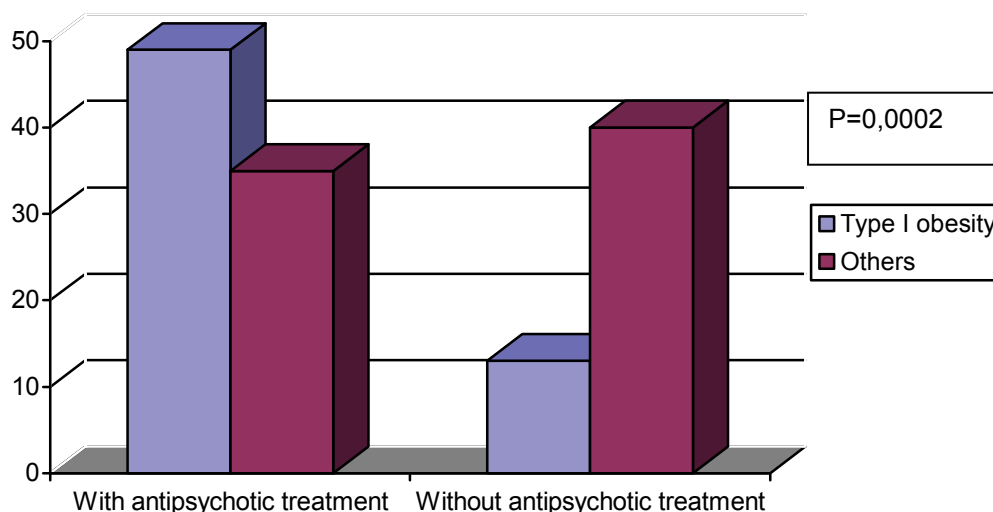


Fig. 3. Distribution of bipolar patients according to antipsychotic treatment

Among the atypical antipsychotics used to treat mania, ziprasidone and aripiprazole are relatively neutral towards weight gain. It is important to be notified that using drugs from this class, medical complications may occur even in the absence of obesity (6). Risperidone produces fewer difficulties on glucose utilization compared with olanzapine and clozapine (6). From antiepileptic drugs used only lamotrigine didn't cause weight gain, didn't increase risk of diabetes, dyslipidemia and other components of metabolic syndrome. Other drugs used to treat bipolar disorder, including lithium; valproate and some antidepressants have been associated with increased risk of obesity.

Most weight gain occurred during the acute illness phase rather than in maintenance therapy. An increased BMI score could be correlated with the severity of depression measured by Hamilton scale, also observed by Fagiolini (5). Although several studies have found a significant obesity in bipolar patients (4,5,9) is difficult to discriminate if obesity is secondary to medications used to treat bipolar disorder or due to disease per se (11). Antipsychotic drugs are associated specifically with central-type obesity, which is a risk factor for diabetes, hypertension and cardiovascular disease but an important role in the development of this specific type of body fat distribution may be related to the existence of high cortisol levels in depressed patients. Besides medicines depressive symptoms may lead to obesity themselves by depressed mood and low activity levels. "Atypical" symptoms as hyperphagia, hypersomnia, and compulsive need for carbohydrates and sweets have been found more frequent in bipolar than in the unipolar depression and can cause weight gain in a row. In terms of affective disorder, weight variations may be associated with lower self-esteem and psychological problems as negative body representation, things that can exacerbate depressive symptoms, and thus creates a vicious circle. Overweight and obese individuals, especially if they also have a psychiatric disorder are more frequently discriminated.

Thyroid dysfunctions associated with bipolar spectrum disorder are serious problems. In addition to medical morbidity associated with thyroid dysfunction, emotional stability and emotional states are

linked to a proper functioning of the hypothalamic-pituitary-thyroid axis. In general, patients with thyroid diseases have higher rates of: panic disorder, simple phobia, obsessive-compulsive disorder, major depressive disorder, bipolar disorder, cyclothimia than the general population (10). This could not be confirmed in this study because only 7% of women and 4.5% of men were diagnosed with a thyroid disease. Bipolar women had a higher rate of thyroid co morbidities than men. Rates are much lower than found by Baldassano (2) who reported rates of co morbidities of 26, 9% in women and 5.7% in men. The reason should be on the one hand and the existence of subclinical thyroid dysfunction and on the other hand under diagnose.

Hypothyroidism is the most common manifestation of thyroid dysfunctions, and the most common psychiatric symptoms associated with it are cognitive dysfunction and depressed mood. On the other hand, increased levels of thyroid hormones can cause dysphoria, anxiety, restlessness and emotional lability. Subclinical hypothyroidism may influence the diseases outcome even in the context of normal results of hormone determinations. Clearly, all patients with affective disorders should be tested for thyroid dysfunction and in the context of high TSH levels with normal T4 levels they should be considered for augmentation with thyroid hormones.

Because overweight and obesity are associated with diabetes, many of the risk factors described above remain valid. The prevalence of diabetes has been reported to be 3 times higher in bipolar patients (9.9%) than in the general population (3.4%) (3). High levels of plasmatic cortisole associated depression may lead to insulin resistance but CNS vascular lesions in diabetic patients may contribute to the development of mania. Another hypothetical link between diabetes and bipolar disorder refers to the transmission of intracellular signals mediated by glycogen synthetase kinase 3 beta (GSK-3 β) whose altered function plays an important role in insulin resistance. Lithium at therapeutic doses inhibits brain GSK-3 β , phenomenon that attenuates cell apoptosis and leads to secondary neuroprotective effect (7). From our 124 patients prospectively followed for 4 years, 32 were diagnosed with type II diabetes and 6 with type I diabetes. The diagnosis of diabetes was more common in bipolar patients with alcohol abuse.

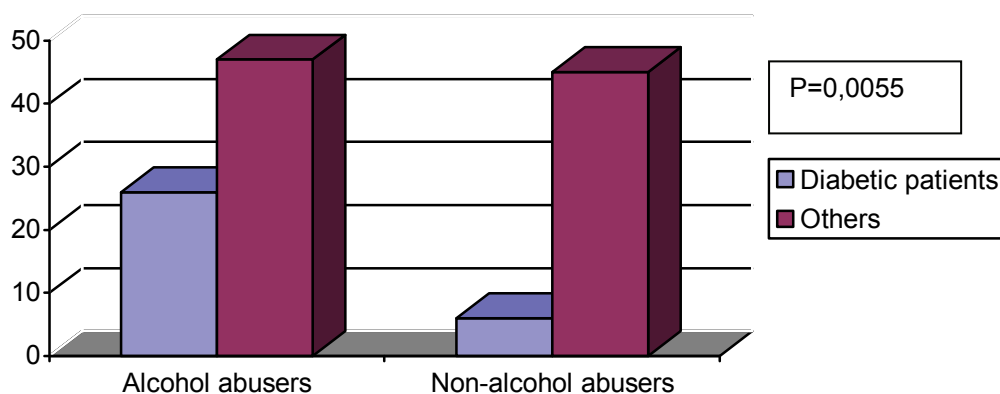


Fig. 4. Frequency of alcohol abuse in bipolar patients with diabetes

Diagnosis of diabetes in the bipolar group was statistically correlated with both ethanol abuse and antipsychotic treatment.

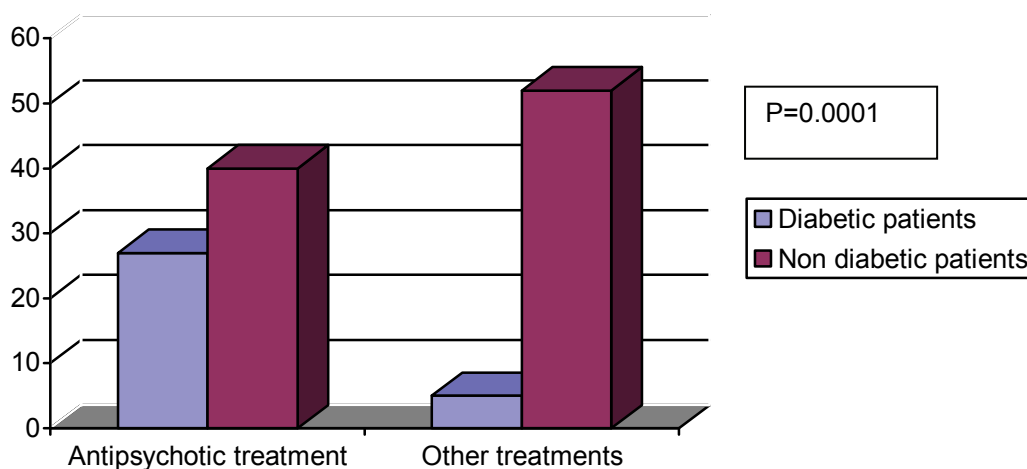


Fig. 5. Frequency of antipsychotic treatment in bipolar patients with diabetes

Conclusions

Obesity, abnormal glucose metabolism and dyslipidemia are risk factors for cardiovascular disease and one of the reasons why patients with bipolar disease had a higher mortality than the general population. Most drugs used to treat mania are both associated with weight gain and the appearance of other components of metabolic syndrome as insulin resistance and dyslipidemia. Olanzapine and clozapine were the most commonly used antipsychotics in the group studied for the treatment of manic episodes and the most associated with metabolic side effects. Antipsychotic drugs were associated specifically with central-type obesity, which is a risk factor for diabetes, hypertension and cardiovascular disease but an important role in the development of this specific type of body fat distribution may be related to the existence of hypercortisolemia in depressed patients. Other drugs used to treat bipolar disorder, including lithium; valproate and some antidepressants have been associated with increased risk of obesity. Besides drugs depressive symptoms may lead to obesity themselves, an increased number of depressive episodes correlated with increased risk of obesity. Thyroid diseases are diagnosed late, usually in the treatment resistant phase of mania or depression. Bipolar women had a higher rate of thyroid co morbidities than men. Medication adjustment in patients with somatic co morbidity should be made with caution to a complex patient easily exposed to toxic side effects. Using atypical antipsychotics such as aripiprazole and quetiapine, with specific mood stabilizer is needed, for reducing metabolic side effects and for good relapse prevention.

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THE NEURO-PSYCHOLOGICAL IMPACT OF THE EXCESS OF THYROID HORMONES IN THYROTOXIC OSTEOPOROSIS

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Abstract

The effects of the thyroid hyperfunction on the central nervous system consist of a nerve hyperexcitability that will interest both components of the nervous system, enhancing not only the somato-psychological activity but also the neuro-vegetative reflectivity, with an appropriate response to the various effector organs. In thyrotoxicosis, there is an accelerated bone remodeling, characterized by an imbalance between bone formation and bone resorption, which will result in bone loss and increased risk of osteoporotic fractures, all these being caused by thyrotoxic osteoporosis. The thyrotoxic osteoporosis study group included 26 patients aged between 40 and 60.

Key words: nervous system, thyrotoxic osteoporosis, thyroid hormones.

Introduction

Thyroid hormones play an important role in normal growth and development of the central nervous system during fetal life and early in the postnatal life. Myelination and neuronal branching processes (axonal and dendritic) are fundamentally influenced by the excess or deficit of thyroid hormones secretion. The thyroid gland begins to function in humans in the fourth month of intrauterine life and is involved in the maturation of certain nervous centers. The hypothyroidism installed during the development of the nervous system will reduce the number of neurons and neuronal endings and will slow down the process of myelination. In terms of neuro-psychological phenomena, mental retardation of varying degrees, often reaching up to the stage of irreversible cretinism occurs. The effects of thyroid hyperfunction or exogenous administration of thyroxine on the nervous system are: increased excitability, emotivity and response capacity, with shorter latency hyperreflexia, nervousness, tremor, anxiety and insomnia (Molina, 2010; Larsen et al, 2002).

Nerve hyperexcitability will interest both components of the nervous system, increasing not only somato-psychological activity, but also neuro-vegetative reflectivity, with an appropriate response to the various effector organs. The synergism between thyroid hormones and the sympathetic nervous system plays an important role in this context. Some metabolic effects of T4 and especially

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T3, such as: increased basal metabolism, glycolysis, lipolysis and heat production, are similar to those of the simpatico-adrenal catecholamines. Thyroid hormones, although do not influence adrenaline and noradrenaline content of plasma or urine, increase the level of cAMP, the catecholamine biochemical messenger. Because of this fact, it was assumed that T4 and T3 increase tissue responsiveness to circulating catecholamines, activating adenylate cyclase-cAMP system (Chen et al, 2010; Jameson, 2001; Dumont, 2001).

The relationship between thyroid hormones and the sympathetic nervous system seems to be more complex, since they increase the number of beta-adrenergic receptors in heart and vessels and adrenergic blocking agents reduce cardiovascular events in patients with hyperthyroidism. Through this complex mechanism, rate and cardiac output will increase, while the force of contraction of the heart decreases steadily due to an increased protein catabolism, leading to the heart failure in thyrotoxicosis.

Metabolic degradation products increase blood flow especially to the skin tissue in order to meet the increased needs to eliminate excess heat by radiation, sweating and evaporation. The blood pressure, especially systolic blood pressure is slightly elevated. As a result of increasing oxygen consumption and carbon dioxide formation, under the action of thyroid hormones, rhythm and amplitude of breathing are constantly activated. Regarding the gastrointestinal tract, they stimulate both food intake and secretion of digestive juices and intestinal motility, resulting in the well- known hyperphagia and diarrhea of the patients with hyperthyroidism (Bassett, 2003; Donald, 2001; Haulica, 2009).

The relationship of thyrotoxicosis and sympathetic nervous system remains still not fully understood. Recent experiments have revealed that the effects of thyrotoxicosis on glucose can be modulated by sympathetic and parasympathetic liver denervation. Indeed, thyroid hormones stimulate hepatic glucose production via a sympathetic new central pathway. Recent studies have suggested that similar neural routes exist for thyroid hormone analogues (Larsen et al, 2003; Zbranca, 2008; Dunn, 2001).

To summarize, the effects of thyroid hormones on the nervous system are a) hyperfunction with hyperexcitability, aggressiveness, irritability, mental confusion, lability, insomnia and b) hypofunction with apathy, depression, slow thinking, poor attention and reduced emotivity.

The clinical effects of thyroid hormones on bone are incompletely known with some aspects that are very well described, while others remain unclear. A major concern of the last decade was to assess the effects of chronic administration of exogenous thyroid hormones on bone physiology. When thyroid hormones are iatrogenically overdosed, a clinical model comparable with endogenous 'subclinical hyperthyroidism' occurs. Thyroid hormones stimulate osteoblasts, favoring osteoid formation. Excessive secretion of thyroid hormones stimulates osteoclastic activity, resulting in increased bone resorption (Bauer et al, 2001, Meier, 2010).

Osteoporosis and osteopenia are relatively frequently encountered in hyperthyroidism, significantly more than in the euthyroidian population. Causal factors are considered to be: the more intense stimulation of the osteoclasts than of the osteoblasts and the alteration of bone remodeling by the thyroid hormones (Toti, 2007).

Hyperthyroidism is a major cause (but not sufficiently recognized) of secondary osteoporosis. The mechanism of thyrotoxic osteoporosis is represented by the action of excess thyroid hormones on both osteoblasts and osteoclasts, but especially osteoclasts, increasing their activity, resulting in bone loss (Inaba, 2004).

Methods

26 patients with age between 40 and 60 years and a diagnosis of thyrotoxic osteoporosis were selected from the Ambulatory of Endocrinology and from the Clinic of Endocrinology of the County Emergency Hospital of Craiova between 2005 and 2010. 8 patients were diagnosed with Basedow-Graves disease, 6 patients with Autonomous thyroid nodule (toxic Node Plummer) and 12 patients had a diagnosis of Toxic multinodular goiter.

For the etiologic diagnosis, clinical (history, physical exam) and laboratory criteria were used. Hormonal investigations consisted of TSH, FT3, FT4, TRAb measurements. Sampling was performed by venous puncture and serum level evaluation was performed in three authorized laboratories. ELISA (Enzyme-Linked Immunosorbent Assay) or immunochemical detection by electrochemiluminescence, depending on the type of laboratory and its equipment, and hormonal values obtained were related to dosing kits. The ELISA method for determining the pituitary, gonadal and thyroid hormones is represented by a competitive immunoassay with the enzyme linked in solid phase. Patient serum hormone competes with an enzyme that is conjugated to the antibody situs of a pearl with a monoclonal antibody. The amount of hormone in the serum is inversely proportional to the amount of the conjugated enzyme of the pearl.

Immunochemical tests with detection by electrochemiluminescence (ECLIA) uses for labeling organic compounds (complexes of ruthenium, osmium, etc.) that electrochemically generates light. Light emission is electrically initiated by applying a voltage to the immune complex (which includes Ru complex) attached to the streptavidin coated microparticles.

The advantage of the electrical initiation of the chemiluminiscent reaction is that the whole reaction can be precisely controlled in terms of time and position. By controlling the time, light emission can be delayed until either the immune response or the enzyme-catalyzed reaction occurs. ECLIA (Electrochemiluminescence Immunoassay) can be used to determine pituitary, thyroid and gonadal hormones. Evaluation of bone mineral density to detect osteoporosis was made by X-ray dual absorptiometry. Dual X-ray absorptiometry (DEXA) is considered the most reliable method to

measure bone density (mass), in order to determine the osteoporosis risk. It was made using the MEDIX 90 equipment at Phoenix Medical Center. Based on Fast Digital Beam and the Pencil Beam safety and precision technology, Medix 90 provides optimum in resolution and scanning time.

Results

1. Basedow-Graves Disease

Out of the 8 patients with Basedow-Graves disease, 5 had between 40 and 50 years and 3 were between 50 and 60 years old.

In the cases included in our study, clinical examination showed a wide range of clinical signs and symptoms belonging to the thyrotoxic syndrome.

Most of the patients included in the study (7 out of 8) showed a characteristic habitus: restlessness, nervousness, alert mimics and gestures.

All patients exhibited different specific symptoms: nervousness (7 patients), emotional lability (6 patients), insomnia (5 patients), aggressiveness (4 patients), restlessness (6 patients), physical asthenia (5), frequent stools (6), weight loss (7), thermophobia (7), and sweating (6).

All patients had neurological disturbances as showed by variable tremor of the extremities, from discrete shaking until visible tremor at rest (3 of 8 patients).

Sensory disturbances (hyperacusia) were inconsistently observed in the studied group.

2. Autonomous thyroid nodule (toxic Node Plummer)

We identified by clinical examination 6 patients with Toxic thyroid nodule, 4 between 40 and 50 years and 2 cases between 50 and 60 years

All 6 patients included in our study showed a wide spectrum of clinical signs and symptoms belonging to the thyrotoxic syndrome. Thus, patients exhibited specific symptoms for thyrotoxicosis: nervousness (4 patients), emotional lability (4), insomnia (5), physical fatigue (3) patients, weight loss (4 patients), thermophobia (4), and sweating (2).

All patients had neurological disorders objectified by tremors of the extremities, most tremors of low intensity (4 patients).

3. Toxic multinodular goiter

The 12 patients with Toxic multinodular goiter had between 40 and 50 years (5 patients) and between 50 and 60 years (7 patients).

All patients included in our study showed clinical signs and symptoms belonging to the thyrotoxic syndrome, but of moderate intensity. Thus, the specific subjective complaints were: irritability (8 patients), nervousness (4), excessive emotion (4), amnesia (3), distributed attention (3), insomnia

(8), physical asthenia (5), weight loss (5), agitation (7), thermophobia (6) and sweating (4). All patients had neurological disorders objectified by tremors of the extremities, most tremors of low intensity (3 patients) – Table 1.

Table 1. The percentage of patients by type of symptoms

Signs and symptoms	Basedow-Graves disease	Autonomous thyroid nodule	Toxic multinodular goiter
Nervousness	88%	67%	34%
Insomnia	63%	84%	67%
Physical asthenia	63%	50%	42%
Thermophobia	88%	67%	50%
Sweating	75%	34%	34%
Neurological disorders	38%	67%	25%
Weight loss	88%	67%	42%

Hormonal measurements:

TSH was dosed in all patients, with values $<0.27 \mu\text{UI/mL}$ (normal range is between 0.27 to 4.2 $\mu\text{UI/mL}$). 13 patients had a TSH value below 0.005 $\mu\text{UI/mL}$, 3 patients had TSH values ranged from .006 to 0.1 $\mu\text{UI/mL}$ and the remaining 10 had TSH values between 0.1 to 0.2 $\mu\text{UI/mL}$ (Fig.1).

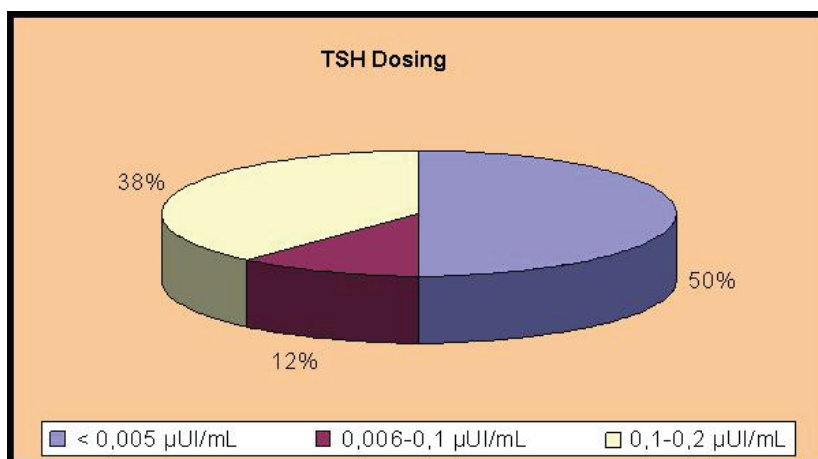


Fig. 1. TSH in thyrotoxic osteoporosis

FT4 (free thyroxine) was also dosed in all patients. The results were constantly over 22 pmol/L (normal range is 12-22 pmol/L). 12 patients had values between 23 and 30 pmol/L, 5 patients had values between 30-40 pmol/L, 6 patients had values between 40-70 pmol/L and 3 patients had values > 100 pmol/L (Fig.2).

FT3 (free triiodothyronine), was also dosed in all patients showing levels higher than the upper limit (normal range is 3.9 to 6.7 pmol/L). 19 patients had values between 6.8 and 20 pmol/L, while the remaining 7 had values over 20 pmol/L (Fig.3).

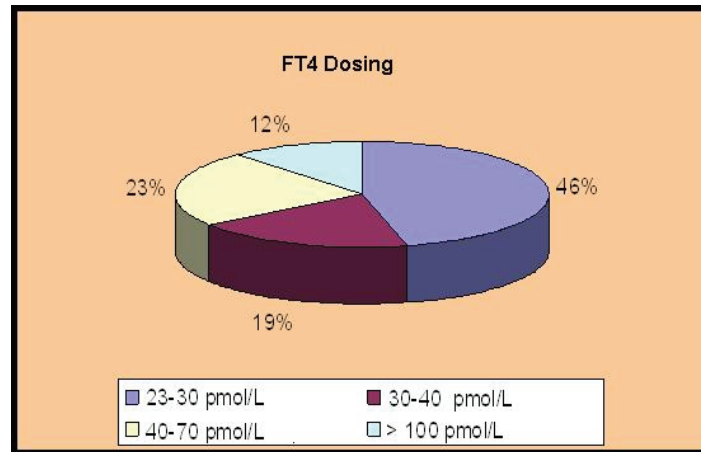


Fig. 2. FT4 in thyrotoxic osteoporosis

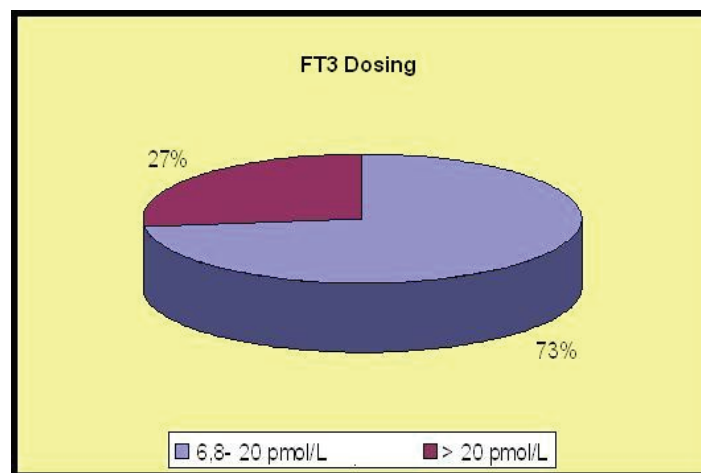


Fig. 3. FT3 in thyrotoxic osteoporosis

TSH receptor antibodies (TRAb) were determined in the patients diagnosed with Basedow Graves’s Disease and all 8 determinations were positive (reference values: negative <1 U/mL, clear = 1 to 1.5 U/mL, positive > 1.5 U/mL)

Discussion

Most patients with thyrotoxic osteoporosis had neuro-psychiatric symptoms that were characteristic for osteoporosis, depending on the thyrotoxicosis etiology. Thus, the highest severity was observed in the patients with Basedow-Graves disease, followed by the patients with Toxic Node Plumer and Multinodular Toxic Goiter, respectively.

All patients included in our study showed a wide spectrum of clinical signs and symptoms of neuro-psychological syndrome belonging of thyrotoxicosis (hyperexcitability, aggressiveness, nervousness, mental confusion, lability, insomnia, tremors of the extremities) in varying degrees of intensity.

The intensity of neuro-psychiatric manifestations was positively correlated with FT3 (free triiodothyronine) (7 patients with values > 20 pmol/L, all showing high nervousness, irritability and visible emotional lability).

TSH was negatively correlated with the presence and intensity of neuro-psychiatric events for FT4 and we could not establish any correlation.

Recent studies have shown that behavioral changes occurring in hyperthyroidism may progress to a nonspecific psychotic illness with bizarre delusional thoughts, usually of a paranoid nature. Therefore, cognitive clouding suggests that the psychotic changes are directly correlated with very high levels of FT3. In patients with thyroid storm, delirium, restlessness, and agitation can appear acutely.

Conclusion

In thyrotoxicosis, regardless of the clinical forms, the first line of treatment consists in the cancellation of the excessive production of thyroid hormones in order to suppress their metabolic and visceral effects.

The particularity of the neuro-psychiatric manifestations of thyrotoxic osteoporosis consists in the specific manifestations of osteoporosis: pain, functional impotence and / or pathological bone fracture.

Complex biological effects of thyroid hormones on central nervous system are incompletely understood, which is a reason for further approaching the study of neuro-psychiatric manifestations of thyrotoxic osteoporosis.

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THE ROLE OF ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF BIPOLAR DISORDER

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Abstract

The biologic treatment is essential in the management of the bipolar disorder, with a decisive impact in the course of this disorder. The medical treatment is represented by mood stabilizers, conventional and atypical antipsychotics, antidepressants. Mood stabilizers and conventional antipsychotics were for a long time the first line treatment in bipolar disorder, but currently these tend to be replaced by atypical antipsychotics. The use of novel antipsychotics is a therapeutic option with highly superior efficacy for bipolar disorder both for the acute periods and for the maintenance and prevention of recurrences.

Ensuring early and wide access to atypical antipsychotics for the patients with bipolar disorder can produce an important improvement in their life quality, but also a decrease in direct and indirect costs over medium- and long-term.

The present study attempts to evaluate the weight of the atypical antipsychotics in succeeding to improve the course of disorder, in reducing the frequency and severity of recurrences, with positive consequences on the social impact, on the direct and indirect costs, in comparison with conventional antipsychotics.

Key words: bipolar disorder, atypical antipsychotics, conventional antipsychotics.

Introduction

The bipolar disorder is part of the category of mood disorders, subsequently reframed as manic-depressive psychosis and then further as manic-depressive disorder. It is a chronic condition in which patients experience manic or hypomanic episodes and depression with relative mood stability between episodes. It is associated with cognitive difficulties and behavioral disorders, and in severe cases patients may also show psychotic symptoms. It represents the third cause for mortality among the young population aged between 15-24 years, 25% of the bipolar patients having at least one suicidal attempt during their life (Keck et al. 2001). At the same time it is the sixth cause for disability among the population aged 15-44 years and the fourth cause for disability among the neuro-psychiatric disorders (The World Health Organization, 2002).

Several psychiatric comorbidities are associated with bipolar disorder: a) substance abuse in 60% of the patients (NIMH, 2000) with 46% having alcohol addiction and 40% having drug addiction

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(Evans, 2000); b) anxiety disorders such as panic disorder, social phobia or obsessive-compulsive disorder; c) impulse control disorders – gambling or kleptomania; d) attention deficit and hyperactivity in around 11% of the bipolar children (Evans, 2000). Cardiovascular (coronary alteration in almost half of bipolar patients and high blood pressure in one third - Garcia-Portilla et al. 2008) and metabolic diseases (obesity in two thirds and diabetes in 26% of the bipolar patients - Regenold et al. 2002) are the major somatic comorbidities.

All these premises together with the social implications raise the direct and indirect costs of the disorder. If in 1985, in the United States, the total costs associated with bipolar disorder were estimated at 20.8 billion dollars and in 1990 at 30.4 billion dollars, they increased in 1991 to 45 billion dollars, out of which 84.5% being the indirect expenses (37.8% due to incapacity to work, 6.7% due to illness pensions, 6.7% costs due to institutionalization, 17.8% due to suicide and 13.3% due to general care) (Rice, Miller, 1995; Wyatt, Henter, 1995). The costs for a usual manic episode reach 11.720 dollars in the US, while for the treatment-resistant patients they increase to 624.785 dollars. During one year, the costs for newly diagnosed cases are estimated at 24 billion dollars (Begley et al. 2001). In the United Kingdom, the direct costs for the treatment of the bipolar disorder amount 2 billion pounds per year or 6900 pounds per person, while the indirect costs due to work incapacity are around 1.510 million pounds (Das Gupta et al. 2002).

Methods

The main objective of this study was the Evaluation of long term evolution of patients with bipolar disorder type I, treated with conventional and atypical antipsychotics, compared with those treated only with atypical antipsychotics. As the second aim we investigated the relationship between individual characteristics and the type of affective episode within each sample.

This a retrospective study of a sample of patients (N=100) diagnosed with bipolar disorder type I according to DSM-IV-TR criteria (Diagnostic and Statistical Manual for Psychiatric Disorders, Fourth Edition, American Psychiatric Association, 1994) based on the records of the Mental Health Centre (MHC) Craiova between 1990-2009.

The inclusion criteria were a) informed consent; b) diagnosis of bipolar disorder type I according to DSM-IV-TR criteria, with at least one affective, manic or mixed episode with or without psychotic elements, congruent or incongruent with mood; c) residence in Dolj county; d) records evidence between 1989-2008 and continuation after this period and e) completeness of data. The exclusion criteria were the refusal of participation, reduced compliance for the maintenance treatment between episodes and a diagnosis of Axis II personality disorder according to DSM-IV-TR.

The recorded variables were gender, age, residence, educational level, marital status, occupational status, age of onset, number, type and duration of the affective episodes, duration

of stay, type of antipsychotic – conventional (AC) or atypical (AA) and associated treatments (mood stabilizers or antidepressants).

The instruments used for the evaluation were the SCID-I (Research Version) Structured Clinical Interview for DSM Disorders and the NIMH Life Chart for Recurrent Affective Illness.

Based on the type of antipsychotic, two groups of patients resulted from the total sample. Group A (n1 = 50) with patients with bipolar disorder type I, still registered at the MHC Craiova in 2009, who were treated with conventional antipsychotics and then with atypical antipsychotics for periods between 54 and 240 months. Group B (n2 = 50) with patients with bipolar disorder type I, still registered at the MHC Craiova in 2009, who were treated from the onset only with atypical antipsychotics for periods between 12 and 120 months.

Results and discussions

Within group B, the average of affective episodes per year was 0.77, lower than the average of affective episodes per year for the entire treatment period in group A (1.1), but also lower than the average of affective episodes per year for the treatment with conventional antipsychotics of patients in group A (1.38) and compared with the average of affective episodes per year for the treatment with atypical antipsychotics of patients in group A (0.83) (Fig. 1).

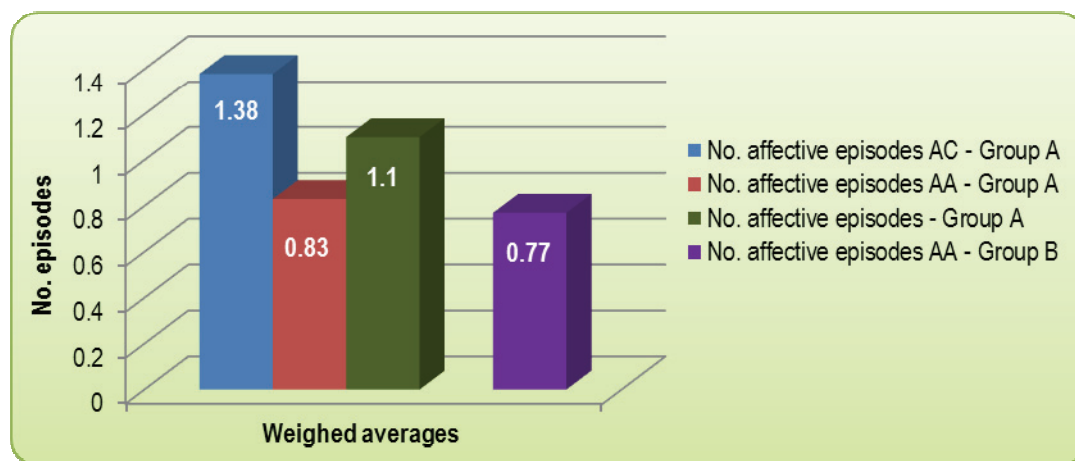


Fig. 1. The average number of episodes of illness in group A and group B

The therapy for bipolar patients with atypical antipsychotics from the onset resulted in the reduction of affective recurrences with 44.2%, compared with the treatment with conventional antipsychotics, while the switch from conventional to atypical antipsychotics determined also a decrease in the number of affective episodes with 39.85%. Globally, the recurrence in group B was 30% lower compared with group A. The decrease in affective recurrences, in the case of atypical antipsychotics, is determined by the increase in the relapse time of good quality remissions, compared with conventional antipsychotics, allowing for a complete social and professional and family reintegration, a determining factor in the reduction of affective recurrences. The superiority

of atypical antipsychotics in the reduction of affective recurrences, including the rapid cycling and resistant types is in accordance with the results of the clinical studies (Bastiampillai et al. 2010; Carta et al. 2006; Das Gupta et al. 2002; Ferreira et al. 2008; Ketter et al. 2010; Smulevich et al. 2005; Tohen M et al. 2006; Vieta E et al. 2003; Vieta E et al. 2005).

Considering the depressive episodes per year, in group B the average was 0.27 episodes/year, lower than the average number of depressive episodes per year for the entire treatment period for patients in group A (0.4 episodes/year), but also lower than the average for the period of treatment with conventional antipsychotics in group A (0.44 episodes/year) and compared with the average number of depressive episodes per year for the period of treatment with atypical antipsychotics from group A (0.33 episodes/year) (Fig. 2).

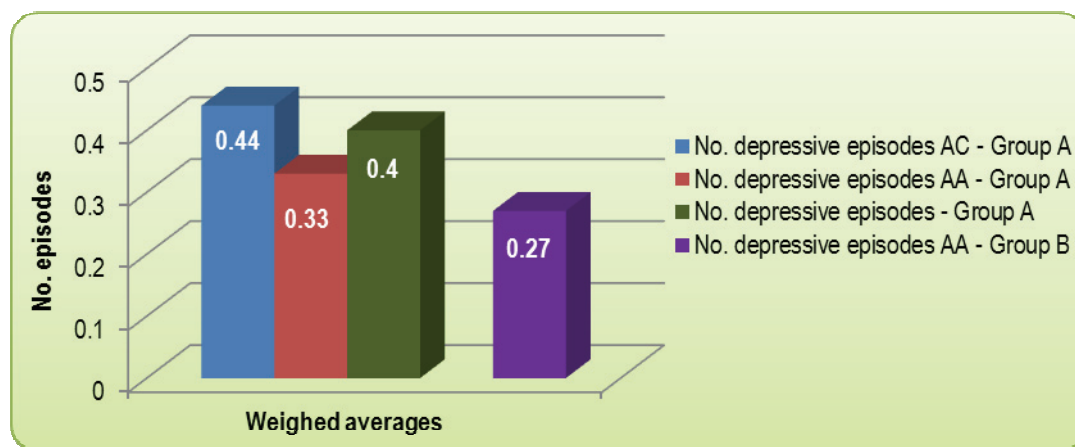


Fig. 2. The average number of episodes of depression in group A and group B

Consequently, the treatment with atypical antipsychotics from the onset of the disorder generates a 38.6% reduction of the recurrence of depressive episodes than with conventional antipsychotics, and the change of conventional with atypical determines the reduction of depressive recurrences by 25%. Globally, the recurrence of depressive episodes was 32.5% lower in group B, compared with group A. This result is in accordance with the specialized literature; the conventional antipsychotics can generate depression, increasing the number of depressive recurrences, while the atypical antipsychotics have an antidepressant effect through their mood stabilizing action, determining the reduction of depressive recurrences (Begley et al. 2001; Shelton RC et al. 2004; Tohen et al. 2005). The average of the number of manic-hypomanic episodes/year in group B was 0.32 episodes/year, lower than the average number of manic-hypomanic episodes for the entire treatment period on the patients in group A, 0.38 episodes/year, lower than the average number of manic-hypomanic episodes/year for the treatment period with conventional antipsychotics for patients in group A, 0.57 episodes/year, but higher than the average number of manic-hypomanic episodes/year for the treatment period with atypical antipsychotics of patients in group A, 0.23 episodes/year (Fig. 3).

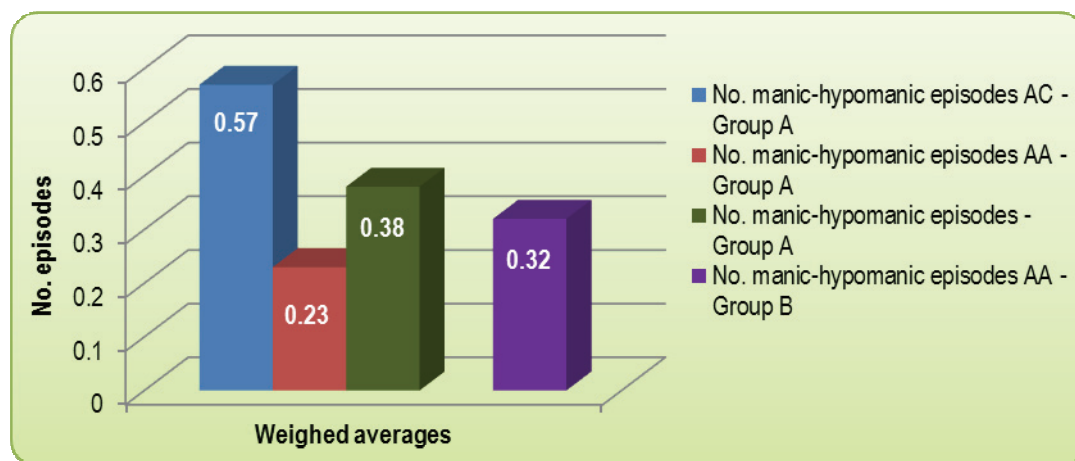


Fig.3. The average number of manic-hypomanic episodes in group A and group B

Consequently, the treatment with atypical antipsychotics from the onset determines a recurrence of the manic-hypomanic episodes 43.86% lower than conventional antipsychotics, and the change of conventional with antipsychotic determines the decrease in manic-hypomanic recurrences by 59.65%. Globally, the recurrence of manic-hypomanic episodes was 15.79% lower in group B, compared with group A. As a paradox, the recurrence of manic-hypomanic episodes in the treatment period with AA in group A was 28.15% lower than in the AA treatment period in group B.

The anti-manic effect of atypical antipsychotic is thus very well emphasized by the decrease in the number of manic recurrences on changing from conventional to atypical antipsychotic, in group A. This result is in accordance with the clinical studies that proved the superior efficacy of atypical antipsychotics in the treatment of acute episode of mania, compared with the conventional ones (Keck et al. 2007; McIntyre et al. 2005; McIntyre RS et al. 2010; Sachs et al. 2002; Thomas et al. 2008; Tohen et al. 2003; Vieta et al. 2005).

Within group B, the average in the number of mixed mood episodes per year was 0.19/year, lower than the average number of mixed mood episodes/year for the entire treatment period for patients in group A, 0.31/year, but also lower than the average of mixed mood episodes/year for the treatment period with conventional antipsychotics, 0.36/year and the average of mixed mood episodes/year for the treatment period with atypical antipsychotics in the patients from group A – 0.27/year (Fig. 4).

The treatment with atypical antipsychotics from the onset determines a mixed episodes recurrence that is 47.22% lower than with conventional antipsychotics, and the change from conventional to atypical determines the reduction of mixed recurrences by 25%. Globally the recurrence of mixed episodes was 38.7% lower in group B, compared with group A. As in the case of manic-hypomanic episodes, the superior efficacy of atypical antipsychotics compared with conventional ones is in accordance with the results from clinical studies (Keck et al. 2007; McIntyre et al. 2005; McIntyre et al. 2010; Sachs et al. 2002; Thomas et al. 2008; Tohen et al. 2003; Vieta et al. 2005).

Within lot B, the average number of hospitalization days/year was 1.33 days/year, lower than the average of hospitalization days/year for the entire treatment period for patients in group A, 2.2 days/year, but also compared with the average of hospitalization days/year for the treatment period with conventional antipsychotics for patients in group A, 2.91 days/year and compared with the average of hospitalization days/year for the treatment period with atypical antipsychotics for patients in group A, 1.45 days/year (Fig. 5).

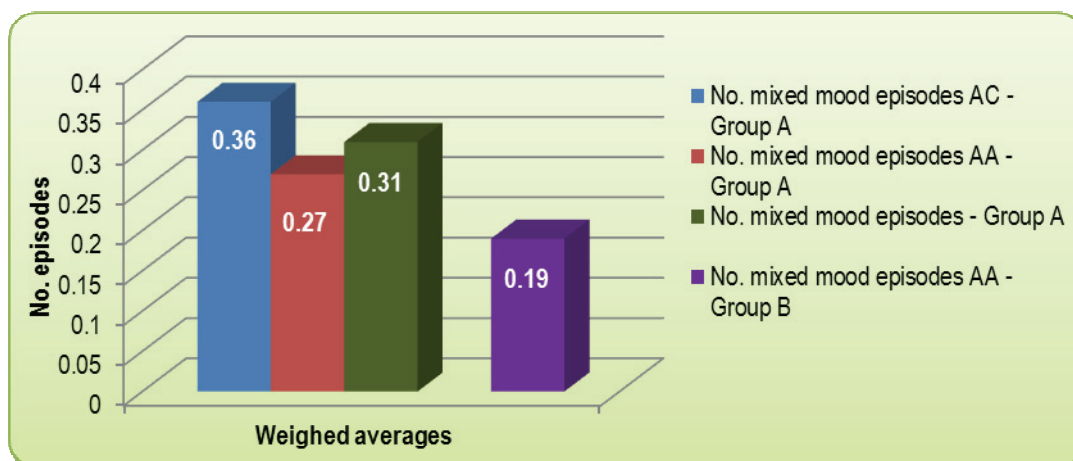


Fig. 4. The average number of mixed mood episodes in group A and group B

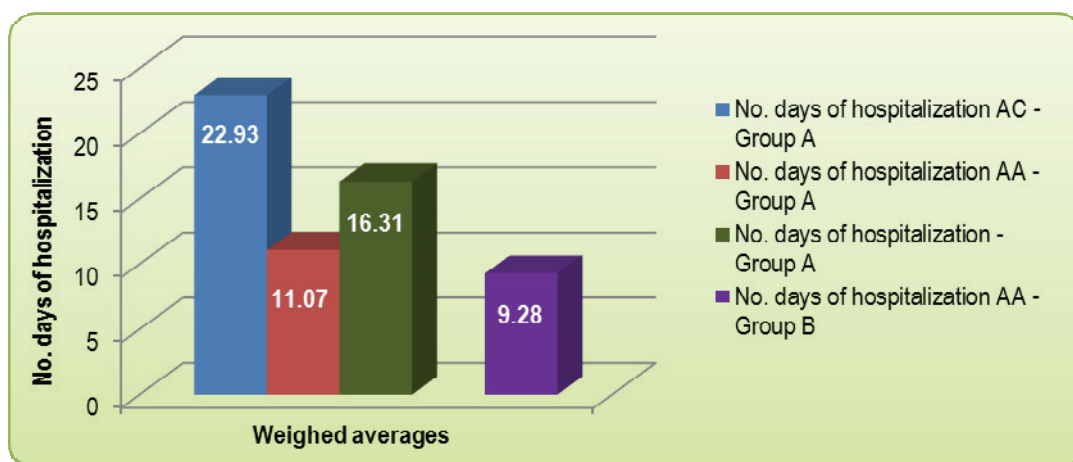


Fig. 5. Average number of days of hospitalization in group A and group B

The treatment with atypical antipsychotics on disorder debut determines a decrease in the duration of hospitalization by 59.53% compared with conventional antipsychotics treatment, and the switch from conventional to atypical determines the reduction in hospitalization by 51.72%. Globally, the duration of hospitalization was 43.1% shorter in group B compared with group A. The faster effect of atypical on mood stabilization, the reduced number of side effects: sedation, concentration difficulties, extra-pyramidal phenomena, determine the reduced duration or even need for hospitalization and allow for a faster and better quality social-professional and family reinsertion. Through the significant reduction in hospitalization duration, the efficiency – cost rate is increased

in the favor of atypical antipsychotics, the hospitalization cost and temporary work incapacity having the largest weight in the costs for treatment of bipolar disorder (Begley et al. 2001; Das Gupta et al. 2002; Rice et al. 1995; Wyatt, Henter, 1995).

Conclusions

The treatment with atypical antipsychotics, compared with the treatment with conventional antipsychotics followed by treatment with atypical antipsychotics, in the patients with bipolar disorder type I, has reduced significantly the statistical average number of episodes/year. By direct comparison between the treatment periods with conventional and atypical antipsychotics from onset, the result obtained is a statistically significant reduction in the relapses/recurrences.

The average number of hospitalization days/year recorded in the patients treated from the onset with atypical antipsychotics was significantly lower than for the patients treated initially with conventional antipsychotics and then with atypical antipsychotics. The switch from conventional antipsychotics to treatment with atypical antipsychotics determined in the evolution of group A a significant reduction of the average number of hospitalization days.

The use of novel atypical antipsychotics represents a therapeutic option with highly superior efficacy for bipolar disorder type I both for the acute periods and for the maintenance and prevention of recurrences. Ensuring early and wide access to atypical antipsychotics for the patients with bipolar disorder type I may produce an important improvement in their life quality, but also a decrease in direct and indirect costs, on medium and long term.

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