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Adult ADHD and affective temperament: a cohort study

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SCHOOL OF MEDICINE

Thesis

ADULT ADHD AND AFFECTIVE TEMPERAMENT:
A COHORT STUDY

by

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M.D., Pontificia Universidade Catolica do Parana, 2002

Submitted in partial fulfillment of the requirements for the degree of Master of Science 2017
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DEDICATION

This thesis work is dedicated to my wife, Vanessa, who has been a constant source of support and encouragement during the challenges of my academic path and life. I am truly thankful for having you in my life.
ACKNOWLEDGMENTS

I would like to express my sincere gratitude to my mentor Prof. Dr. Nassir Ghaemi for the continuous support of my master study and research, for his patience, motivation, enthusiasm, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my master study.

Besides my mentor, I would like to thank the rest of my thesis committee: Prof. Dr. Derick Vergne, Prof. Dr. Janice Weinberg, for their encouragement, insightful comments, and hard questions.

My sincere thanks also goes to Dr. Marco Antonio Bessa, for offering me also important comments and review during the writing process.
ADULT ADHD AND AFFECTIVE TEMPERAMENT: A COHORT STUDY

SIVAN MAUER

ABSTRACT

It has been suggested that adult attention-deficit/hyperactivity disorder (ADHD) may reflect affective temperaments, which involve mild manic and/or depressive traits as part of one’s personality. Such innate traits are associated with poor attention. Stimulant medications, given for ADHD, can worsen manic symptoms, thereby worsening attentional symptoms paradoxically, by worsening the underlying mood condition that causes poor attention.

This study examines the nature of response to stimulant medication in subjects with affective temperament (Cyclothymia, Hyperthymia, Dysthymia).

A retrospective cohort study was conducted of 87 subjects from Tufts Medical Center Mood Disorders Program. Subjects were included if they had ever been prescribed stimulant medications. Prior diagnosis of adult ADHD, or not, also was assessed. This sample was assessed using TEMPS-A scale to measure affective temperaments, and the CGI-I scale to assess clinical change in mood/anxiety and attention/cognition.

Data analysis was conducted using descriptive statistics and stratification. This study has several limitations. Researchers and subjects were not blinded; all subjects received stimulants, with no non-stimulant control group; and treatment response was
assessed retrospectively. Nonetheless, no such data exist in the scientific literature previously, and thus this pilot data adds to our present knowledge.

61% of the sample had an affective temperament (using the strictest definition of 75% or more TEMPS items endorsed). Of these, the most common was cyclothymic (40%) followed by hyperthymic (24%).

The main treatment results were that most patients (55%) had no effect on mood/anxiety, but a large number (43%) had worsening mood/anxiety symptoms. 37% had mild or moderate improvement in cognition.

Stratified by ADHD diagnosis, stimulant effects were somewhat better with, than without, ADHD diagnosis, for cognition but not for mood/anxiety. In ADHD subjects, 49% had worsening mood and/or anxiety symptoms, while 44% had some improvement in cognition/attention. In non-ADHD subjects, 30% had worsening mood and/or anxiety symptoms, while 30% had some improvement in cognition/attention.

In conclusion, we found that most people (61%) treated with amphetamine stimulants identified in a mood specialty clinic were diagnosable with affective temperaments, especially cyclothymia. Amphetamine stimulant worsened mood/anxiety symptoms in about one-half of subjects, and improved cognition symptoms only about one-third subjects. Prior ADHD diagnosis was associated with somewhat improved cognitive, but not mood/anxiety, outcomes. These results suggest that amphetamine stimulant treatment in an affectively ill population may have harmful mood/anxiety effects, and has only partly beneficial cognitive effects.
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LIST OF ABBREVIATIONS

ADHD……………………………………..Attention Deficit Hyperactive Disorder
AMA………………………………………….American Medical Association
CGI-I………………………………….Clinical Global Impression Improvement
DSM………………………………..Diagnostic and Statistical Manual of Mental Disorders
FDA……………………………………….Food and Drug Administration
GWAS………………………………..Genome Wide Association Studies
ICD……………………………………..International Classification of Diseases
REDCap……………………………….Research electronic data capture
STROBE…………………………….Strengthening the Reporting of Observational studies in Epidemiology.
TEMPS-A…………………………..Temperament Evolution of Memphis, Pisa and San Diego auto questionnaire.
INTRODUCTION

Contemporary American psychiatry bases diagnoses on the DSM-III through 5 system, which is characterized by being purely descriptive of symptoms (1). Further, overlapping symptoms are present in many diagnoses, and are accepted as “comorbidities” (2). This leads to the scenario where mood symptoms, for instance, can cause anxiety or inattention, and yet patients are diagnosed with multiple diagnoses of mood disorders, anxiety disorder, and attention deficit hyperactivity disorder (ADHD). In contrast, before the current DSM approach began to be used in 1980 with the 3rd revision, a century or more of psychiatric research was based on the classic medical tradition of diagnosing as few conditions as possible (3). Thus, since mood conditions can cause anxiety and inattention, only mood diagnoses would be made even if anxiety and inattention symptoms are present. Further, diagnoses were based on the course of illness and other factors, like genetics, not just symptoms alone, as in the DSM system (4).

This contrast plays in current psychiatric practice around the diagnosis of ADHD in particular, since inattention can be caused by other illnesses (such as mood and anxiety conditions). In this paper, we specifically address the concept of affective temperaments, which were seen for much of the 19th and 20th centuries, as mild versions of mood illnesses. Manic-depressive illness was the overarching mood illness, with either manic or depressive episodes as its main feature (5,6). In those patients and their relatives, it was noted that many persons had constant mild manic or depressive symptoms all the time, as part of their personalities (7). This was called affective temperaments, with mild manic symptoms
In recent years, the diagnosis of ADHD has been extended from children to adults in the 5th revision of DSM (DSM-5) (8), and it is increasingly diagnosed and treated with amphetamine, a potent central nervous stimulant. The latter agents have been shown to cause mania or worsen bipolar illness (9,10). In this study, we sought to identify and describe the potential mis-attribution of ADHD diagnosis and treatment to individuals with dysthymic and cyclothymic temperaments. We will then comment on the potential worsening of mood and anxiety in misdiagnosed individuals as well as on the lack of improvement in cognitive domains in misdiagnosed ADHD individuals with temperamentally significant dysthymia and cyclothymia.

**Affective temperaments defined**

At one level affective temperament can be defined as mild version of mood states or sub-affective personality conditions or sub-syndromal manifestation of the illnesses (11,7). It includes basic differences in personality traits and energy levels as expressed in sleep patterns and sexual and social behaviors or work related activities. The three basic temperaments are described as following:

Hyperthymia involves mild manic symptoms as part personality. Such persons are high in energy, need less sleep than most people (often 4-6 hours), have high sex drives, are highly social, extroverted, often workaholics, fast thinking, possibly higher consumption of alcohol, cigarettes, coffee, spend more money, and are often humorous. They are described...
as the life of the party, fun, loving and can also engage in risk taking or reckless behaviors that others often avoid, such as skydiving or bungee jumping. They dislike routine and are spontaneous. They can be quite anxious and inattentive (12,13).

Dysthymia is a mild depressive state as part of one’s personality. Such persons are characterized as low energy, need more sleep than most people (9-11 hours), have low sex drive, prone to excessive worrying. It also includes preoccupation with personal failure. They avoid risk-taking behaviors and are devoted to routine. They can be quite anxious but not inattentive (12,14,15).

Cyclothymia involves a constant alternation between mild manic and depressive states on a day- to –day, or a few days at time, basis that fail to meet duration for major affective syndromes. Such persons go up and down in mood and energy as well in activity levels. They are generally extroverted, exhibiting high productivity, as well as highly social and risk-taking behavioral tendencies. Sometimes, those people are unpredictable and spontaneous. The core features in the majority of them include lability, anger and irritability. Inattention is very common (14).

The prevalence of mood temperaments relies on the cut off of 50 or 39 items of Temperament Scale of Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A); a validated research scale for temperaments. Both of them have a very high and similar coefficient alpha. In statistics Cronbach’s alpha is used to estimate the reliability of a scale. It can be viewed as the expected correlation of two scales that measure the same construct. Cyclothymic 0.88 for 50 items and 0.91, for 39 items. Hyperthymic, 0.81 and 076. Dysthymic, 0.76 and 0.81 (12,16,17). In one study, they were defined as 75%
or more items being endorsed on the TEMPS-A. Using this definition, about 40% of subjects in a mood disorder clinic met the definition of cyclothymia. About 15% met the definition of hyperthymia and 10% were definable as dysthymia. About 50% of the subjects did not have any full mood temperament. If the cut off is put at lower threshold of 50% of items, then the majority of subjects with mood conditions, like bipolar illness and major depression disorder meet the definition of mood temperament (18). Population prevalence studies are limited, but genetics studies that have looked at mood temperaments have noted that they are the most frequent finding in family members of persons with mood illness. These family members do not have full-blown depressive or manic episodes. (19).

Thus, since mood conditions occur in about 5-10% of the general population in the Unites States (major depressive disorder and bipolar disorder) (20,21). One could infer that affective temperaments occur in a large number; perhaps a conservative estimate would be 10-20% of the general population in the United States. In many cases, affective temperament occurs by themselves, meaning that no other diagnoses are present. In other cases, they occur as the baseline temperament in between full depressive or manic episodes in persons with mood illnesses.

This study has one particular outcome of interest. That outcome is stimulant response in two domains. Mood/ anxiety and cognition/attention assessed using the Clinical Global Impression Scale –Improvement (CGI-I), in a population using any amphetamine approved by the FDA for ADHD treatment and affective temperament. Understanding that this is new approach to look at the inattention symptom shedding light on a possible new pathway of knowledge to approach the treatment and ADHD diagnosis. How is the
amphetamine response in this population going to reflect on the treatment of ADHD in the future? The hypothesis is that amphetamine would worsen in the mood/anxiety domain and at least be ineffective in the cognitive domain.
METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (22). Charts of all outpatients treated in the Tufts Medical Center Mood Disorders Program were reviewed to identify all subjects treated with any amphetamine or stimulant medication approved by FDA to treat ADHD (Methylphenidate, dextroamphetamine, dexamethylphenidate, lisdexamfetamine). Also, another inclusion was presence of a completed TEMPS-A scale (50 items or 39 items). This scale was validated in more than 25 languages, to access temperament types as cyclothymic, dysthymic and hyperthymic, as explained in more details in the introduction (23). 87 subjects with 18 years or above from a population of 770 patients treated in the program were included in this study (Figure 1). Their charts were reviewed for the following clinical and demographic variables: age, sex, ethnicity, marital status, employment, education level, family history, psychosis and mania history, the average time of amphetamine use, and diagnosis after evaluation in Mood Disorders Program. Tufts Medical Center Institutional Review Board approval to conduct this chart review was obtained.

Amphetamine response was accessed in relation to cognition/attention and in relation to mood/anxiety by a Clinical Global Impression improvement (CGI-I) rating scale. The CGI-I ratings were ascertained retrospectively at the time of chart review by 2 psychiatrist/researchers with expertise in mood disorders (Sivan Mauer MD and Nassir
Ghaemi MD). After completing independent ratings, consensus was established for each patient for any ratings that differed. The CGI-I scale assesses the extent of clinical change in the patient at the point of assessment compared with baseline, using a 7 point range from “very much improved” 1 to “very much worse” 7 (24). From May to July 2016 data was collected using REDCap, a research electronic data capture (25).

**Statistical Analyses**

Statistical analyses included descriptive statistics, stratification, and chi-square test to compare the treatment response between the two groups in both domains (mood/anxiety and cognition). TEMPS-A was used as a dichotomous measure with 50% and 75% of cut off. The sample was stratified between subjects that had ADHD diagnosis and those who did not have any official diagnosis of ADHD in their lives. All analyses were made using “R” version 3.2.4 software (26).
RESULTS

Table 1 provides clinical and demographic characteristics of the sample. About one-half of the sample was diagnosed with ADHD at some point in the past, and on-half was not. The majority of both groups were white and unemployed. The ADHD group was younger. Most of the non-ADHD group lived alone and had higher education level. Family history of bipolar disorder was present in half of subjects in both groups. Average time of amphetamine use was more than double in the ADHD group. After research-based diagnostic evaluation, about 90% of the sample was diagnosed with bipolar disorder.

26% of the ADHD group had at least one manic/hypomanic episode caused by amphetamine use versus 16% in the non-ADHD group. 21% of subjects overall had amphetamine-related manic/hypomanic episodes.

Using the 50% item threshold, temperaments were common, with highest prevalence for cyclothymia, followed by hyperthymia and then dysthymia in the ADHD group. In the non-ADHD group, there was also high prevalence of cyclothymia, followed by dysthymia and then hyperthymia. Very few people were not diagnosable with any temperament. Using the 75% item threshold, the most prevalent temperament in both groups was cyclothymia, the prevalence of hyperthymia in the ADHD group was almost double the non-ADHD group, and 45% of non-ADHD subjects and 32% of ADHD subjects did not have any kind of temperament. In the total sample 61% had an affective temperament using the definition of 75% TEMPS-A items endorsed. Of these, the most
common kind of temperament was cyclothymic (40%) and hyperthymic (24%). Affective temperaments are not mutually exclusive; there is less overlap with higher cut-off thresholds.

Regarding treatment response, using the CGI-I, in ADHD subjects 49% showed worsened mood/anxiety; 44% showed no benefit for cognition/attention (Table 2, Figure 2, and Figure 3). In non-ADHD subjects 30% had worsened mood/anxiety, and most of this group also showed no benefit for cognition/attention, with somewhat more than one-quarter showing some improvement (Table 2, Figure 4 and Figure 5). In the total sample 43% had worsened mood/anxiety symptoms, and 37% of subjects had mild or moderate improvement in cognition (Table 2, Figure 6, Figure 7). The chi-square statistic in both domains is small (5.39 in mood/anxiety and 2.04 in cognition) meaning that in this sample the amphetamine response is not associated with ADHD diagnosis (Table 2).
DISCUSSION

This is the first study that correlates the three main types of temperament and amphetamine response. Three kinds of temperament, especially cyclothymia, were prevalent notably in this sample. Amphetamine response was poor, with worsening of mood/anxiety in most cases, and little benefit for cognition/attention in our sample. About one-fifth of patients with affective temperaments experience amphetamine-related manic episodes. One clinical implication of these results is that adult ADHD diagnosis, and/or prescription of amphetamine stimulants, may occur in some cases in the setting of misdiagnosis of affective temperaments. Another possibility could be that cyclothymia is a common temperament in both bipolar disorder and ADHD.

There is only one prior study of temperament association with ADHD diagnosis, with similar findings. In that case-control study in Norway, 586 clinically diagnosed subjects with adult ADHD were compared to 721 controls. Using the 50% item cut off TEMPS definition, 71% of subjects with ADHD and 13% of controls were classified as having cyclothymic temperament. In both studies the “comorbidity” with mood illness are higher in the ADHD group, being present in almost 80% (27).

There are no prior studies of amphetamine outcomes related to affective temperaments and ADHD. There are prior studies of amphetamines in bipolar disorder and ADHD comorbidity, with some showing efficacy, and some showing no benefit (28–31). An example of the latter type of study is a randomized crossover trial of methylphenidate and placebo combined with aripiprazole in 16 children and adolescents with bipolar
disorder and ADHD, in which methylphenidate was not more effective than placebo (32). These results would be consistent with our finding that most of subjects of both groups did not have improvement in cognition.

No prior study has assessed mood/anxiety effects, separately from cognitive effects, with affective temperaments and ADHD. Few studies of bipolar disorder and ADHD comorbidity exist which assess mood outcomes with amphetamine stimulants for mood. For example, one retrospective chart review with 16 adult patients with bipolar illness who were prescribed methylphenidate for any reason found improvement in mood related symptoms (33). A prospective cohort study from the same group with 14 adult patients with bipolar depression met a decrease in depression symptoms in the Hamilton depression scale (34). The only other study to assess amphetamine-related mania in adults reported that it occurred in 40% of subjects (n=137) with bipolar disorder (mean age 38.8 years) (10). In a retrospective chart review of 82 bipolar children (mean age of 10.6 years), 24% of the sample had manic or hypomanic episodes with amphetamines (35), similar to our study where 21% of total sample experienced mania or hypomania with amphetamines. Also almost half of subjects in the ADHD group experienced worsened mood symptoms with amphetamines. Only 2% of subjects experienced mood or anxiety improvement in the ADHD group, and none in the non-ADHD group.

This study has several limitations. The sample was not randomized; the data are open, uncontrolled and retrospective. Former psychiatrist/clinicians made the diagnosis of ADHD clinically, without using validated diagnostic interviews. The non-controlled design of this study did not allow for comparisons to subjects not treated with amphetamines. The
naturalistic context of treatment, especially concomitant use of other medications, could introduce confounding treatment effects in the assessment of amphetamine treatment response or side effect perception. Since 78% of subjects were Caucasian, these results may not be generalizable to other ethnic groups.

In conclusion, a relationship appears to exist between cyclothymic and hyperthymic temperaments in subjects treated with amphetamines. Stimulant response was neutral in the majority of these subjects in relation of mood/ anxiety or cognition attention, with some worsening in subjects diagnosed with ADHD. These results may indicate that adult ADHD is misdiagnosed in some persons who have hyperthymic or cyclothymic affective temperaments. Further amphetamines seem mostly ineffective or even harmful in these patients. Future research could build on these pilot data with larger samples and more valid research designs, and with non-stimulant control groups. These could include case-control studies or prospective cohort studies with large numbers of subjects, with and without ADHD diagnosis, with and without stimulant treatment, and assessed with validated scales for affective temperaments and ADHD, as well as validated scales for treatment response. Further, randomized clinical trials could be conducted in patients with affective temperaments of cyclothymic and/or hyperthymia, randomized to stimulant treatment versus placebo, to assess mood and cognitive treatment response. A comparator arm of mood stabilizer treatment could be included as well to see if such treatment is equal to, better than, or worse than stimulant medications in this population.
<table>
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<th>Not ADHD N=44</th>
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<tr>
<td>Age (SD)</td>
<td>30.1±11.7</td>
<td>39.8 ±14.2</td>
<td>35±13.8</td>
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<tr>
<td>Gender Male (%)</td>
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<td>Marital status- single (%)</td>
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<td>25- BA</td>
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<tr>
<td>Lives alone (%)</td>
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<tr>
<td>Dysthymic 50(%)</td>
<td>41</td>
<td>48</td>
<td>45</td>
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<td>Cyclothymic 50(%)</td>
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<td>Diagnosis BD (%)</td>
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<td>89</td>
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<td>Manic episode (%)</td>
<td>26</td>
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<tr>
<td>Average time use</td>
<td>236.5 ±205</td>
<td>108 ±128.7</td>
<td>180±185.7</td>
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<td>amphetamine weeks (SD)</td>
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Table 2 Percentages of amphetamine response in Cognition and Mood/anxiety

<table>
<thead>
<tr>
<th></th>
<th>Total (87) CGI Mood/Anxiety</th>
<th>Total (87) Cognition</th>
<th>Non-ADHD (n=44) CGI Mood/Anxiety</th>
<th>ADHD (n=43) Mood/Anxiety</th>
<th>ADHD (n=43) CGI Cognition</th>
<th>Non-ADHD (43) Cognition</th>
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<tr>
<td>Improvement (%)</td>
<td>2</td>
<td>37</td>
<td>0</td>
<td>7</td>
<td>44</td>
<td>29.6</td>
</tr>
<tr>
<td>No Change (%)</td>
<td>55</td>
<td>63</td>
<td>64</td>
<td>44</td>
<td>56</td>
<td>70.4</td>
</tr>
<tr>
<td>Worse (%)</td>
<td>43</td>
<td>0</td>
<td>36</td>
<td>49</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\( \chi^2 = 5.39 \ p = 0.07 \)

\( \chi^2 = 2.04 \ p = 0.36 \)

\( \chi^2 \) = Chi-Square test
Fig. 1 Subject’s inclusion/exclusion criteria flowchart

- **770 Subjects from Tufts Mood Disorders Program**
- **93 Subjects Amphetamine used and TEMPS-A**
- **3 Subjects excluded. TEMPS-A Incomplete**
- **90 Subjects**
- **3 Subjects excluded. Under 18 years**
- **87 Subjects included**
Figure 2

CGI Mood/Anxiety ADHD

- No change: 44.00%
- Minimally Worse: 21.00%
- Much Worse: 23.00%
- Very Much Worse: 5%

- Very Much Improved: 0%
- Much Improved: 7.00%
- Minimally Improved: 0.00%
Figure 3

CGI Cognition ADHD

<table>
<thead>
<tr>
<th>Perception</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Very Much Improved</td>
<td>0%</td>
</tr>
<tr>
<td>Much Improved</td>
<td>21.00%</td>
</tr>
<tr>
<td>Minimally Improved</td>
<td>23.00%</td>
</tr>
<tr>
<td>No change</td>
<td>56.00%</td>
</tr>
<tr>
<td>Minimally Worse</td>
<td>0.00%</td>
</tr>
<tr>
<td>Much worse</td>
<td>0.00%</td>
</tr>
<tr>
<td>Very Much Worse</td>
<td>11%</td>
</tr>
</tbody>
</table>
Figure 4

CGI Mood/Anxiety Non ADHD

- Very Much Improved: 64.00%
- Much Improved: 9.00%
- Minimally Improved: 16.00%
- No Change: 5%
- Minimally Worse: 5%
- Much Worse: 5%
- Very Much Worse: 5%
Figure 5

CGI Cognition Non-ADHD

Figure 6

CGI Mood/Anxiety Total
Figure 7

CGI Cognition Total

- Very Much Improved: 0%
- Much Improved: 24.00%
- Minimally Improved: 13.00%
- No change: 63.00%
- Minimally Worse: 0.00%
- Much Worse: 0.00%
- Very Much Worse: 0.00%

The chart shows the distribution of CGI Cognition Total scores among participants.
## LIST OF JOURNAL ABBREVIATIONS

<table>
<thead>
<tr>
<th>Journal Abbreviation</th>
<th>Full Title</th>
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<td>Am J Psychiatry</td>
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EDUCATION

2001 M.D. Medicine PUC - PR, Brazil
2015- M.S. Clinical Investigation Boston University

POSTDOCTORAL TRAINING

Internship and Residencies:
2002-2004 Resident in Psychiatry Clinica Heidelberg/BR
2014-2015 Resident in Children Psychiatry Hospital Pequeno Principe/BR

Fellowships:
2012-Present Mood Disorder Program Tufts Medical Center

LICENSURE AND CERTIFICATION

2002 Brazilian Medical Board
2004 Brazilian Board of Psychiatry
2012 Brazilian Board of Children Psychiatry

ACADEMIC APPOINTMENTS

2005, Supervisor, Psychiatry, Clinica Heidelberg - Brazil
2008-2010, Researcher, Psychiatry Institute, Universidade de São Paulo (USP) - Brazil

HOSPITAL APPOINTMENTS

2004-Present, Partner/Psychiatrist, Instituto Kraepelin Psychiatry Clinic - Brazil
2014-2015, Assistant Psychiatrist, Hospital Pequeno Principe - Brazil
TRAINING OF GRADUATE STUDENTS/POST DOCTORAL

2002-2005 Specialization in Couple and Family Therapy ISBL – Brazil
2011 Attended PhD Courses: Scientific Methodology, Journal Club, and translational methodology in schizophrenia. UNIFESP-Brazil

TEACHING RESPONSIBILITIES

2005-2006, Psychiatry Residence, Psychiatry Department, Clinica Heidelberg-Brazil

PROFESSIONAL SOCIETIES

2002-Present Brazilian Medical Association
2002-Present Parana Medical Association
2004-Present Brazilian Psychiatry Association
2004-Present Parana Psychiatry Association

OFFICE AND COMMITTEE ASSIGNMENTS IN PROFESSIONAL SOCIETIES

2008-2013, Vice – Chairman, Paraná State Psychiatry Association - Brazil

MAJOR RESEARCH INTERESTS

Major research interests are in diagnosis of psychiatry illnesses specially mood disorders, dementia, schizophrenia, and validity of ADHD diagnosis. Also lithium has an important role in my research work.

EDITORIAL BOARDS AND ACTIVITY

2014-Present Member of Psychiatry Letter’s Editorial Board

*BIBLIOGRAPHY

Refereed:


**Books chapters:**
