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International Journal of Psychiatry in Clinical Practice

International Journal of

Psychiatry in Clinical Practice

Volume 11 Number 4 December 2007

EDITORS

David Baldwin
Siegfried Kasper

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Chapter in book

Friedman MJ, Southwick SM. Towards a pharmacotherapy of PTSD. In: Friedman MJ, Charney DS, Deutch AY, editors. Neurobiological and clinical consequences of stress: From normal adaptation to post-traumatic stress disorder. New York: Lippincott-Raven; 1995, p 469.

Complete book

Judd FK, Burrows GD, Lipsitt DR, editors. Handbook of studies on general hospital psychiatry. Amsterdam: Elsevier; 1991.

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- *Predictors of antidepressant response: A selective review.* Dodd S. and Berk M., 2004
- *Anxiety disorders: does one treatment fit all?* Baldwin D., 2004
- *A comparison of olanzapine versus risperidone for the treatment of schizophrenia: a meta-analysis of randomised clinical trials.* Mudge et al., 2005
- *Jaundice and hepatic enzyme induction during lamotrigine therapy in a bipolar II patient.* Selek et al., 2005

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Taylor & Francis
PO Box 12 Posthuset
NO-0051 Oslo, Norway
Tel: (+47) 23 10 34 60, Fax: (+47) 23 10 34 62,
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Key words:

Psychiatry, Neuropsychopharmacology, Mental health,
Neuropsychiatry, Clinical Neurophysiology,
Psychophysiology, Psychotherapy, Addiction,
Schizophrenia, Depression, Bipolar Disorders and Anxiety

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The *International Journal of Psychiatry in Clinical Practice*, ISSN print 1365-1501, online 1471-1788, is published quarterly by Informa Healthcare/Taylor & Francis AS. Visit our home page for more information: www.tandf.no/ijpcp

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SUBSCRIPTION INFORMATION

Annual subscription rates for volume 11, 2007: Institutions (print & online): US\$485, institutions (online only): US\$460, individuals (print & online) US\$179. Air speed postage and online access included. Supplements are supplied free of charge to all subscribers.

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Indexed in: Cambridge Abstracts, Chemical Abstracts Service, Current Contents (Clinical Medicine), EMBASE (Excerpta Medica), ISA Alerting Services, Online Review and SUBIS Current Awareness in Biomedicine, PsycINFO, PsycLIT, ClinPSYC, Science Citation Index – Expanded and Psychological Abstracts.

International Journal of Psychiatry in Clinical Practice (USPS permit number 021349) is published four times a year, in March, June, September and December. The 2007 US institutional subscription price is US\$485.

Periodicals postage paid at Jamaica, NY by US Mailing Agent Air Business Ltd, c/o Priority Airfreight NY Ltd, 147-29 182nd Street, Jamaica, NY 11413, USA.

US Postmaster: Please send address changes to MPCP, Air Business Ltd, c/o Priority Airfreight NY Ltd, 147-29 182nd Street, Jamaica, NY 11413, USA.

Typeset by Datapage International Ltd., Dublin, Ireland.

Printed in Great Britain on acid-free paper by Hobbs the Printers.

EDITORIAL

A number of original articles as well as a short article and a case report are presented in this issue together with the abstracts of the posters as well as symposia of this year's International Forum of Mood and Anxiety Disorders (IFMAD) Meeting, to be held in Budapest, Hungary, from 5 to 7 December 2007.

Axelrod and colleagues addressed the important question of how to improve evaluation of the clinicians' understanding of the quality of a traumatic event. This understanding is a necessary first step requirement for a diagnosis for post-traumatic stress disorders (PTSD) as defined by DSM-IV-TR. The seeming lack of clarity was evaluated by having fictional scenarios rated as traumatic or not by mental health clinicians. It emerged that psychiatrists and psychologists consistently rated events less likely to be traumatic than did social workers. Colleagues with less professional experience were more likely to indicate that an event was traumatic. Research clearly indicates that criterion A1 for PTSD that includes both the intensity of a stressful event and one's emotional reaction to the stressor needs to be refined to assist clinicians in objectively demarcating events consistent with the trauma and those that are not considered traumatic according to the existing definition.

In the second article the topic of depression in diabetic outpatient population is covered by Daly et al. Based on the results in 92 patients it emerged that the Major Depressive Disorder (MDD) affects one in every 4 patients with diabetes and that there is a association between depression and hyperglycemia, as well as impairment in disease self-management. The authors emphasized that combination screening strategies for both diabetes and major depression may facilitate prompt detection of depression as well as providing an ongoing measure to specific psychiatric symptoms.

Hrdlicka and Dudova studied 47 schizophrenic patients with an average age of 16.5 years and assessed the therapeutic effects and tolerability of risperidone. It emerged that risperidone in doses between 2 and 6 mg has been found to be an effective and safe treatment for schizophrenia and other related psychotic disorders in adolescents in the sample obtained in a Czech population. Moreover, it was suggested that the sensitivity of the adolescent population to side effects seems generally to be higher than in the adult population.

Castle and colleagues from Australia investigated the effects of group intervention for bipolar disorders. It emerged that a psychosocial group based on intervention for Bipolar I and II patients which was delivered as an adjunct to treatment as usual

resulted both in a reduction of relapse and improvement in functionality. Furthermore, it could be concluded that group intervention is a cost-effective way of delivering psychosocial treatments.

The question of animal-assisted therapy (AAT) has been studied by Iwahashi and his Japanese colleagues. AAT is used a therapeutic tool to improve social, emotional as well as cognitive functioning in psychiatric patients in Europe and America. It seems that this is a new concept for Asian countries. It emerged that Japanese patients liked dogs and horses and understood that the contact with these animals helped them in various psychiatrically important aspects. The colleagues indicated that this study helps to develop the AAT program in Japan. However, it does not seem that it needs to be developed in Japan only but also in a number of psychiatric facilities in Europe.

Topiramate-induced psychotic exacerbation was discussed in a case-report and literature review from Karslioglu et al from Turkey. The colleagues used a dosis of 100 mg/d of topiramate in an undiagnosed schizophrenia patient. The discontinuation of topiramate did not result in an improvement of the psychotic symptomatology so treatment with olanzapine (10 mg/d) was initiated and titrated upwards to 30 mg/d. Topiramate is used for its weight-losing properties as well as possible treatment of negative symptoms. Clinicians should be aware of this possible side effect that of course needs to be further substantiated in controlled studies.

The 7th International Forum of Mood and Anxiety Disorders (IFMAD) Meeting will be held for the first time in Budapest, Hungary, from 5 to 7 December 2007. IFMAD has become an important forum for the exchange of ideas on the latest development in psychiatric treatments where international experts can address some of the important topics in the field of mood and anxiety disorders in an informal atmosphere. The scientific contributions are grouped in main symposia as well as poster presentations. The abstracts of this meeting are presented in this issue and give the opportunity for a focused discussion of new data in a constructive and productive environment. The topics address issues on how to improve signal detection in placebo-controlled studies as well as problems underlying suicide attempts in psychopharmacological trials and Treatment Resistant Depression (TRD). The treatment of depression and anxiety in the "post-SSRI" era and the importance of sleep and depression, everyday problems in treating depression with a focus on SNRIs as well defining the boundaries for antidepressant treatment will be elaborated. The topic of pain as a neglected symptom of affective

disorders as well as treatment of the elderly and diagnosis as well as receptor issues in the treatment of mood and anxiety disorders will be discussed.

We do hope that this issue together with the abstracts of the 7th IFMAD meeting will provide

further evidence for a better understanding and treatment of psychiatric patients.

Siegfried Kasper

ORIGINAL ARTICLE

Evaluation of traumatic events as defined by the DSM-IV-TR criteria

BRADLEY N. AXELROD, JOHN GRABOWSKI & LILY TREWHELLA

John D. Dingell Department of Veterans Affairs Medical Center Detroit, MI, USA

Abstract

Objective. We attempted to better evaluate clinicians' understanding of Criterion A1 of Posttraumatic Stress Disorder. **Method.** Approximately 50 mental health clinicians from the Department of Veterans Affairs evaluated 10 scenarios in which potentially traumatic events were described. **Results.** The results found psychiatrists and psychologists to be slightly more conservative in claiming an event was traumatic in comparison to social workers. In addition, events were deemed at a somewhat higher level of trauma for individuals who had less years of experience at the Department of Veterans Affairs. **Conclusion.** These data are presented as the initial step in better understanding the features included in determining whether an event is deemed traumatic according to the DSM-IV-TR criteria.

Key Words: *Assessment, PTSD, Diagnosis, DSM-IV*

Introduction

The psychiatric anxiety disorder named posttraumatic stress disorder (PTSD) first appeared in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980 [1]. The inclusion of this diagnosis was in response to veteran advocates who noted that the mental health symptoms following military trauma occurred in survivors of non-military traumatic events [2,3]. In response to a trauma, a diagnosis of PTSD was observed in the emotional reactions to significant traumatic events that included the triad of symptom clusters that are still used in the most recent version of the DSM (DSM-IV-Text Revision [4]). These symptoms include re-experiencing events, avoidance or numbing, and increased arousal.

Although agreement generally exists regarding the primary symptoms of PTSD, clarification regarding the types of events that might be considered as stressors is needed. For the DSM-III, the criterion for an event to be considered traumatic was "a recognizable stressor that would evoke significant symptoms of distress in almost everyone" and that it was considered beyond the "usual human experience" in terms of the intensity of the event ([1] p. 236). The intent of the definition of a trauma was aimed to identify events such as military combat, rape, earthquakes, floods, confinement in prisoner of war camps, and similar events as being capable of causing PTSD [1].

Since the first definition of PTSD, clarification regarding what events should be considered traumatic has been sought. March [5] provided a literature review of studies to better understand Criterion A. He concluded that an event be deemed as stressful if it were life threatening or associated with physical injury. In addition, though, he opined that an individual's response to such an event must be a form of extreme fear or helplessness. This secondary feature was proposed to be particularly helpful in explaining events that are less than life-threatening but appeared to nonetheless serve as a PTSD stressor. The DSM-IV PTSD task force [6] appeared to follow suit, adopting a two-part definition for a stressor as outlined in Criterion A. The threat aspect of the definition was expanded to include events in which not only death, but the threat of physical injury in self or in others was included. An empirical study found the number of events considered traumatic that might occur in one's life increased with the new criteria [7], including stressors that are less extreme (e.g., separation from spouse) than earlier definitions [8].

The DSM-IV-TR maintains the two-part definition of a stressor that includes exposure to an event and the psychological reaction to it. However, the traumatic stressor can include not only experiencing or witnessing an event, but also being "confronted" with an event. The event can include actual death or injury, or can be related to a seemingly lesser

dangerous “threat to physical integrity to others”. In selecting words from the definition of Criterion A1, a stressor could be witnessing death or experiencing torture. However, it may also result from being told about how someone else was threatened. Even being informed of someone who was in a motor vehicle accident or by simply being present in a war zone regardless of the extent of combat exposure might meet Criterion A1 for a stressful event. The potential event exists for socially inappropriate jokes to be viewed by this definition as meeting the criteria for a traumatic event, according to some authors [9]. The implication of the broadened definition of PTSD stressors is that the intensity of the trauma no longer has to be as severe as initially proposed by DSM-III. Dr. McNally refers to this dilution of the definition as “conceptual bracket creep” in which criteria have been loosened over time [10].

In the course of clinical work in the Department of Veterans Affairs (DVA), it is the responsibility of the clinicians to work with the definitions proposed by current versions of the DSM. Despite the apparently clear criteria for what constitutes a traumatic event, clinical experience has demonstrated inconsistency across clinicians using the same definition. Disagreement in the interpretation of Criterion 1A serves as a departure point for differences of opinion regarding the meeting of diagnostic criteria for PTSD. Less problematic are differences in opinion relating to the re-experiencing, avoidance, or increased arousal associated with the examinee’s claimed stressor. As a result of the lack of agreement across clinicians regarding the definition of a stressor, unreliable diagnoses might be provided for patients seen for evaluation. In addition, there is concern that the identification of an experience as being traumatic is associated with a clinician’s level of training, years of experience, or type of service provided.

In this study, the ability and comparability of Department of Veterans Affairs mental health workers to evaluate fictitious traumatic scenarios was evaluated. The reliability of the ratings as well as other potential factors affecting agreement, were studied.

Method

Requests for participation were made via electronic mail to 300 individuals associated with one of seven Department of Veterans Affairs medical centers in the Midwest. The e-mail document included information regarding the study and a link to an on-line website where the survey was posted. The first screen included an informed consent and participants could exit the anonymous survey at any time during the process. Two weeks after the first e-mail was sent, a reminder was sent to the same 300 individuals, asking those who had not yet done so to participate. At that time 50 people had completed

the study and another 22 individuals subsequently did so.

Participants

In response to the requests, 47 clinicians completed the study. An additional 25 individuals responded, but indicated that they were non-clinical staff. They included social workers ($n=28$), psychiatrists ($n=10$), and psychologists ($n=9$). Relative to the total number of individuals who are clinicians in each of these fields (social workers: $n=111$; psychiatrists: $n=79$; psychologists: $n=51$), the percentage of respondents was comparable between psychologists and psychiatrists ($z=0.78$, ns), as well as psychologists and social workers ($z=1.07$, ns). However, the response rate was significantly lower for psychiatrists relative to social workers ($z=2.13$, $P=0.03$). For each of these groups, the years of service, time in the VA system, type of setting, and services provided are indicated in Table I. The social workers represented a group of individuals who had significantly fewer years in the profession and years at the VA. It should be noted that in our facility, social workers do not offer diagnoses, although they are involved in clinical case conferences where they are present with other clinicians who use the criteria from the DSM-IV-TR to reach diagnoses.

Measures

The 10 scenarios used were written along a spectrum of what the authors believed were definitively traumatic events (e.g., working in graves registration, witnessing civilians being shelled) and definitively not traumatic events (e.g., working for a hostile supervisor, reporting casualties to the Department of Defense). The items are presented in the appendix. Each participant rated the extent to which the scenarios met Criterion A1. The rating was on a five-point Likert scale, ranging from reports that the event was “definitely not traumatic” to “definitely traumatic”. A score of “3” could be considered that an event “may or may not be” traumatic.

Statistical analyses

The relative ratings were compared for each of the scenarios, as well as for the total of all 10 scenarios, via one-way analyses of variance (ANOVA). The inter-rater reliability was assessed via intraclass correlation coefficients of agreement.

Results

The overall reliability for the ratings of 47 participants across the 10 items fell in the Good Range both for agreement across individuals (ICC coefficient of agreement = 0.71) and within individuals

Table I. Background information of participants.

	Psychiatrists	Psychologists	Social workers
Years in profession	20.6 (4.2)	24.2 (7.2)	14.7 (9.8)*
Years at the DVA	9.1 (6.4)	13.9 (9.2)	7.3 (8.8)*
Urban (vs. suburban) setting	60%	77%	44%
Facility is a teaching hospital	40%	88%	46%
Services provided (percentage of respondents in each profession who reported performing each service)			
Assessment	90%	89%	64%
Individual psychotherapy	10%	67%	54%
Group psychotherapy	0%	67%	39%
Medication management	100%	0%	0%

*Social worker was significantly lower than other two groups.

(ICC coefficient of consistency = 0.83). The scores, while wholly acceptable, demonstrate a stronger consistency within an individual in rating the 10 items as opposed to across raters. Such a finding suggests that there is some “examiner bias” in which the participants tend to rate all scenarios at a similar level, be it more conservative or more liberal in identifying an event as being traumatic according to the criterion.

The average rating scores for each of the scenarios, as well as the total score, appear in Table II. Average ratings were significantly higher for social workers in comparison to psychologists and psychiatrists ($F(2, 45) = 6.85$, $P < .003$; $\eta^2 = 0.242$). Overall, the power of this analysis reveals a large effect size [11]. As far as individual items are concerned, this same pattern was only seen for two of the items, while a third item was significantly lower for psychologists in comparison to psychiatrist and social work participants. An examination of moderating variables found no relationship between the overall rating of an event as traumatic and years of providing mental services. However, an inverse correlation ($r = -0.37$, $P = 0.01$) was found relative to years at the DVA and rating scores, consistent with social workers having higher ratings and fewer years in the DVA system. There was no association between level of rating and the type of setting of the DVA medical center or in the services provided by the professionals.

For informational purposes, an exploratory factor analysis was performed for informational purposes regarding the 10 scenarios included in the study. When data from all 72 respondents were entered into an analysis with varimax rotation, three factors emerged with eigenvalues greater than 1.0. The resulting three-factor solution accounted for 66% of the variance among the items. Of interest, from the perspective of understanding the definition of a trauma, the three factors seemed to relate to: (1) experiencing a trauma first hand (items 1, 3, and 4); (2) having an emotional reaction to a trauma this might have occurred (items 5, 6, and 10); and (3) experiences unlikely to be considered traumatic (items 2, 7, 8, 9). Interestingly, it was two of the items that fell in the range of “unlikely to be considered traumatic” that were seen as more traumatic according to social workers in comparison to psychiatrists and psychologists.

Discussion

The present study intended to assess the consistency among professionals in applying Criterion A1 to a variety of stressful events. Although the overall reliability indices indeed indicate comparability on a five-point Likert scale, examination of the variance of many of the items demonstrates the variability that nonetheless exists. Even in experienced clinicians who perform evaluations and treatment of psychiatric

Table II. Average five-point Likert ratings across professional group.

Item #	Psychiatrists	Psychologists	Social workers
1 (helicopter)	3.7 (1.2)	2.8 (1.6)	3.6 (1.1)
2 (cook at base camp)	1.9 (0.6)	2.1 (1.4)	2.8 (1.2)
3 (shelling of civilians)	4.1 (0.9)	3.8 (1.3)	4.2 (0.8)
4 (graves registration)	4.7 (0.5)	3.9 (1.2)	4.7 (0.7)*
5 (concussion)	3.3 (1.4)	3.7 (1.6)	4.2 (1.2)
6 (noise of shells)	2.5 (1.2)	2.4 (1.5)	2.7 (1.3)
7 (hostile supervisor)	1.8 (1.0)	1.1 (0.4)	2.6 (1.5)**
8 (spit on in airport)	1.8 (1.0)	1.6 (1.0)	2.7 (1.4)**
9 (casualty reports)	1.5 (0.7)	1.4 (1.0)	2.7 (0.9)
10 (fear on first night)	3.7 (1.2)	3.1 (1.4)	3.6 (1.3)
Average rating	2.9 (0.6)	2.4 (0.7)	3.3 (0.7)**

*Psychologists were significantly lower than other two groups.

**Social worker was significantly higher than other two groups.

patients, there is variability among clinicians in accepting a stressor as a Criterion A1 traumatic event. An ancillary finding revealed that individuals who are prone to be more lenient in their definition are more lenient across the board, while those who are conservative in defining a PTSD trauma remain so regardless of the stressor.

The confounding effects of level of training (i.e. social work versus psychology or psychiatry) and years of experience (social workers were less advanced) were associated with more lenient interpretations of the definition of a trauma. As a result, events that were deemed definitively not traumatic by the psychologist (e.g., having a hostile work supervisor), fell more in the range of “may or may not be” a traumatic event. It may be possible that because the psychologists and psychiatrists had been practicing longer than the social workers, they incorporated a prior definition of trauma into the current definition. For example, the possibility of requiring an event to be “outside the realm of normal human experience” might remain a core theme for more senior clinicians, even if that DSM criterion no longer exists. In addition, social workers in the Department of Veterans Affairs offer clinical therapeutic services, but do not grant official diagnoses. Their familiarity with the DSM-IV-TR might therefore be less developed.

There are certainly weaknesses in performing a survey study of clinicians. Our response rate was lower than we would have liked in our attempt to capture typical clinical practice. It is our hope that future studies of this kind will be met with a greater number of respondents, thus providing evidence of a more representative sampling. The higher rate of return among social workers compared to psychiatrists might have also biased the conclusions. The confounding effect of years of professional experience is another obvious weakness of this study. With a larger sample, we would be able to control that confound either through sample selection or through statistical control (e.g., analysis of covariance). Third, the authors do not suppose that reading a brief scenario regarding traumatic events offers the same quality of information that one might obtain in a clinical interview. Even so, the purpose was to assess Criterion A1 in the abstract, intentionally disconnected from current symptoms.

As currently written, criterion A for PTSD includes both the intensity of a stressor as well as one's emotional reaction to the stressor. The preliminary factor analysis of the scenarios used in this study appears to capture aspects of the reaction and the stressor as being separate entities. With continued refinements of the definition ongoing, further clarification regarding each of these features is indicated. In fact, specific examples that tap the different aspects of Criterion A1 and A2 might also be provided. Such exemplars would also assist clinicians

in objectively demarcating events consistent with a trauma and those that are not considered traumatic according to the existing definition.

Key points

- The presence of a traumatic event is first-step requirement for a diagnosis of PTSD, as defined by the DSM-IV-TR
- The seeming lack of clarity was evaluated by having fictional scenarios rated as traumatic or not by mental health clinicians
- Mental health clinicians were reliable over time (within individual), but not necessarily in full agreement with each other (between individuals)
- Psychiatrists and psychologists consistently rated events as less likely to be traumatic than did social workers
- Another moderating variable was that individuals with less professional experience were more likely to indicate that an event was traumatic

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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Appendix : Trauma scenarios presented to participants

Read each scenario and determine if it meets the definition for a traumatic event.

Definition of Trauma: “The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others”.

1. Helicopter: I was refueling a hovering helicopter onboard ship. The force from the blades blew me down and nearly pushed me overboard.
2. Cook at base camp: When I was a cook at base camp, I befriended a lot of guys that came in from the field for a few days. As my tour went on, I realized that many of them were not returning. Later in my tour, I discovered that a close friend was sent home in a body bag. After that time, I learned not to ask where people were if they did not return with their squad from the field.
3. Shelling of civilians: My job in the Navy was to watch the shelling through binoculars and direct the big guns to hit the targets. As we were moored offshore once, I observed the shelling of a village in which civilians were running out of their homes, fleeing for their lives.
4. Graves registration: For one afternoon, I was stuck in a dark windowless room with a stack of bodies and body parts. My job was to try to match the body parts to the right soldier and then put them in individualized body bags.
5. Concussion: As a truck driver in a convoy, I was following a full personnel carrier that ran over a landmine. I do not remember the event, but I was told that the personnel carrier and my truck were blown apart. My last memory is of loading the convoy that morning and my next memory is of awakening in a hospital bed a couple days later with my head bandaged.
6. Noise of shells: Shortly after getting to Vietnam, I heard the sound of a significant firefight in which the noise of the shells was deafening. Although I expected to be in combat, that sound was something I had never experienced.
7. Hostile supervisor: While working at HQ under a hostile superior, I was constantly berated by him. He sent me memos and email that were demeaning. He also harassed me by whispering insults and other verbal abuse that marginalized my work. He stated that I could not be trusted and that I should be reprimanded for poor work.
8. Spat on at airport: After serving for one year in Vietnam, I finally finished my tour and made it back to the states. After thinking about returning to The World for 12 months, I couldn't believe that I was actually in an airport in California, ready to fly back home. While waiting for my flight, I smiled at this woman who was also waiting for the plane to board. Rather than smiling back, she looked me up and down and asked, “how many babies did you kill?” Before I knew it, she had spit on me and walked away.
9. Casualty reports: While serving during the Tet Offensive, I was responsible for typing and forwarding letters to the Department of Defense regarding battle casualties.
10. Fear on first night: During my first night in Vietnam, I saw tracers streaking across the sky for much of the night. Charlie was letting us know that he could get us. All I felt throughout that long night was fear, fear, fear.

Note: The phrases prior to each scenario are provided for reference and were not present in the questionnaire.

ORIGINAL ARTICLE

Screening for depression in a diabetic outpatient population

ELLA J. DALY¹, MADHUKAR H. TRIVEDI¹, PHILIP RASKIN² &
BRUCE D. GRANNEMANN¹

Departments of ¹Psychiatry and ²Endocrinology, University of Texas Southwestern Medical School, Dallas, TX, USA

Abstract

Depression occurs twice as often in patients with diabetes and is associated with reduced compliance with exercise, diet, and medications. It is also associated with hyperglycemia and increased diabetic complications. Despite evidence that successful treatment is associated with improved glycemic control, many cases of depression are left untreated. *Objectives.* (1) Evaluate a combination screening strategy in an outpatient population; and (2) explore the association between glycemic control and depressive symptomatology. *Methods.* Ninety-two patients completed the Patient Health Questionnaire (PHQ-2). Patients with a PHQ-2 score ≥ 1 completed the 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR₁₆). Using the QIDS-SR₁₆, a score of ≤ 5 corresponded to normal mood, with scores above 5 corresponding to increasing severity of depressive symptoms. Glycemic control was assessed by glycosylated hemoglobin (HbA1c). *Results.* Using a PHQ-2 cut-off score of ≥ 3 , 37% of the sample screened positive for major depressive disorder (MDD), with an additional 27% reporting sub-threshold symptoms. The depressed group reported significantly more difficulty with reduced interests, insomnia, concentration, self-criticism, energy/fatigue and depressed mood. In terms of glycemic control, there was a marginally significant effect for race and HbA1c. *Conclusion.* The combined PHQ-2 and QIDS-SR₁₆ can facilitate prompt detection of MDD and provide a means of monitoring specific symptoms and progress once treatment commences.

Key Words: Depression, screening, diabetes

Introduction

Major depressive disorder (MDD) is a serious, debilitating illness that affects persons of all ages, races, and socioeconomic backgrounds. Depression also significantly increases the burden of functional impairment from chronic medical illness, while treatment of co-morbid depression reduces disability and healthcare costs. Evidence suggests that depressive symptoms go unrecognized in around 30–50% of patients in primary care [1,2], and general hospital settings [3].

The prevalence of depression among patients with diabetes is twice that of the general population [4]. Depression is significantly associated with hyperglycemia [5], which in turn is linked to the development of diabetic complications [6]. Optimal outcomes in diabetes require diligent attention to diet, exercise, and regular glucose monitoring – requiring motivation, energy, and sustained effort, all of which are often lacking in individuals with depressive illness. Studies show an association between depression and impairments in behaviors such as exercise, diet and adherence to medication [7]. Evidence also suggests

that patients with diabetes and co-morbid depression appear to experience more physical symptoms associated with their diabetes than their non-depressed counterparts [8].

Despite evidence suggesting that successful treatment of co-morbid depression is associated with improved glycemic control [5,9,10], depression screening has not become routine and two-thirds of cases remain untreated [11]. The aim of this study was to (1) evaluate a screening process combining two validated questionnaires that not only assess for the presence of MDD, but also provide a measure of severity of symptoms. Secondary aims of the study were to (2) determine the prevalence of depression in a diabetic outpatient population and (3) determine if there was a significant difference in glycemic control between those who validated depressive symptomatology and those who did not.

Methods

All consenting patients over 18 years old attending a diabetic outpatient clinic were included. Subjects first completed the two-item Patient Health

Questionnaire (PHQ-2) [12]. Those validating the presence of depressive symptoms (i.e. a PHQ-2 score ≥ 1) completed the self-rated, 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR) [13]. Using the QIDS-SR, a score of ≤ 5 corresponds to normal (non-depressed) mood, and scores of 6–10, 11–15, 16–20 and 21+ correspond to a mild, moderate, severe, and very severe range of depressive symptomatology, respectively.

Study participants

Of 100 patients approached about the study, only eight refused to participate. Of the 92 participants enrolled, 89 made up the analyzable sample (three were taking antidepressant medication at the time of screening and were excluded).

The two-item Patient Health Questionnaire (PHQ-2)

This questionnaire enquires about: (1) depressed mood and (2) decreased interest/pleasure within the previous 2 weeks. Scoring ranges from 0 ("not at all") to 3 ("nearly everyday"). Validity of the PHQ-2 has been assessed using an independent mental health interview, with PHQ scores ≥ 3 reported to have a sensitivity of 83% and a specificity of 92% for MDD [12].

The 16-item self-report Quick Inventory of Depressive Symptomatology (QIDS-SR)

This rates symptoms within the past week [13] and is derived from the 30-item Inventory of Depressive Symptomatology (IDS) [14–16] by selecting only items that assess DSM-IV-TR criteria for MDD: (1) depressed mood; (2) concentration; (3) self-criticism; (4) suicidal ideation; (5) interest; (6) energy/fatigue; (7) sleep disturbance; (8) decrease/increase in appetite/weight; and (9) psychomotor retardation/agitation. The QIDS has been compared to the Hamilton Depression Rating Scale (HAM-D) [17] and shown to be an appropriate measure of symptom severity [15].

Results

Sample characteristics

Of the sample analyzed, 66.7% were female with a mean age of 52.7 years (range: 26–74 years). The sample consisted of 46.1% African-Americans, 52.8% White individuals, and 1.1% Asian individuals, with 22.47% of the sample being of Hispanic ethnicity (see Table I).

Of those with a PHQ-2 score ≥ 1 ($n=57$); the mean PHQ score was 3.16 (± 1.8) with a mean QIDS-SR score of 11.25 (± 4.92). Based on a PHQ-2 cut-off score of ≥ 3 , 37.1% (33/89) of those

Table I. Demographics of sample.

	Percent	Mean (SD)
Gender		
Male	33.7	
Female	66.3	
Age		52.8 (11.8)
Marital STATUS		
Married/cohabiting	26.9	
Divorced	33.7	
Separated	12.4	
Single	23.6	
Widowed	3.4	
Race		
African-American	46.1	
Asian	1.1	
White	52.8	
Ethnicity		
Hispanic	22.5	

screened had evidence of MDD, with 27% (24/89) reporting sub-threshold depressive symptoms not reaching the cut-off score for MDD. In terms of gender, of those with scores indicating the likely presence of MDD, 75.8% (25/33) were female, with similar results (79.2% or 19/24) observed in those reporting sub-threshold depressive symptoms (i.e. a PHQ-2 score of 1 or 2), whereas only 46.9% (15/32) of those who did not report depressed mood at all (i.e. PHQ-2 score = 0) were female. Of those with evidence of MDD, 21.2% (7/33) were in the mild range of depressive symptomatology, with 42.4% (14/33), 33.3% (11/33), and 3% (1/33) in the moderate, severe and very severe range respectively based on QIDS-SR₁₆ score.

Race, depression and diabetic control

Seventy-two patients from the sample analyzed had a hemoglobin A1c (HbA1c) level within 10 days of their clinic visit; another 10 patients had a level within the previous 3 months, while six had not had a level for over 3 months (longest interval since last level was 4 months). The mean HbA1c for the sample was 7.44 (1.52 SD), with the mean HbA1c for the Depressed and Sub-threshold depressed groups 7.42 (1.54 SD) and 7.68 (1.35 SD) respectively, compared to 7.29 for those in the Non-Depressed group (i.e. PHQ-2 = 0, $n=32$).

An ANOVA was conducted with both race and presence of depressive symptoms as independent measures, and HbA1c as the dependent measure, in order to test for difference in glycemic control between groups. In spite of a modest sample size, the results of this analysis produced a marginally significant effect for race ($F(2,83) = 3.06$, $P < 0.06$), indicating, as reported previously, that there may be some difference in glycemic control for race/ethnicity [18]. The data suggests that African-American

Table II. Mean HbA1c by PHQ-2 group.

	HbA1c* Levels		
	No depressive symptoms	Depressive symptoms	All
	Mean (SD)	Mean (SD)	Mean (SD)
African-American	6.67 (1.09)	7.29 (1.51)	7.11 (1.41)
Hispanic	8.05 (1.60)	7.98 (1.63)	8.00 (1.58)
White	7.45 (1.93)	7.76 (1.08)	7.61 (1.54)
All	7.29 (1.63)	7.57 (1.45)	

*Hemoglobin A1c.

patients had the best glycemic control, with those of Hispanic ethnicity having the worst control, and Caucasian patients falling somewhere between. Note the one Asian patient was not included in this analysis (see Table II).

Difference in symptom distribution between PHQ-2 groups

As was expected, patients with a PHQ-2 score ≥ 3 validated more items on the QIDS-SR – indicating more severe depressive symptomatology than their counterparts with PHQ-2 scores of 1 or 2. In order to test for difference in the rates of specific depressive symptoms between the two groups, a series of analyses were conducted using Fisher's exact test. Presence of the symptom was defined as ≥ 2 on the QIDS item. The Depressed group endorsed higher rates for initial ($P=0.008$) and late insomnia ($P=0.004$), concentration ($P=0.01$), self criticism ($P=0.009$), and energy ($P=0.002$), as well as depressed mood ($P=0.0000002$) and interest ($P=0.0004$) (see Figure 1).

Discussion

The rates of depression found in the current analysis (37%) are similar to those reported previously

[19–21]. One review reported MDD in up to 20% of diabetic patients (both treatment and community samples) [20]. A recent meta-analysis reports MDD in 11% of individuals with diabetes, with prevalence of depression significantly higher in clinical (32%) than in community (20%) samples [4].

As can be seen in Figure 1, patients in the sub-threshold group presented with a wide array of depressive symptoms. Even though there are significant differences between patients with depressive symptoms that are likely to have MDD and those that are unlikely to have MDD (i.e. the sub-threshold group), those differences may not be obvious. Awareness of specific symptom profiles may be useful to clinicians in terms of identifying patients more likely to develop MDD, even in the absence of reported depressed mood.

In terms of glycemic control, even though there was not a significant difference found between either the depressed or sub-threshold groups and the non-depressed group (i.e. those with a PHQ-2 = 0), this may be due to the small sample size. Looking specifically at race and ethnicity, we did not see a significant difference based on presence of depressive symptoms. However, in our sample there does appear to be an interesting pattern, with African-Americans appearing to have better glycemic control in the absence of depressive symptoms than with depressive symptoms present. In contrast, presence of depressive symptoms appears to have no effect on glycemic control in those of Hispanic ethnicity, despite evidence of overall poor control. Despite similar reports [22], as this difference is not significant, no conclusions can be drawn, with a larger study needed to further explore this issue.

Assessing for the presence depression in the presence of physical disorder can present a diagnostic challenge in the absence of routinely employed screening procedures. Patients with depression often present with overlapping symptoms – including frequent body aches, pain, headaches, gastrointestinal

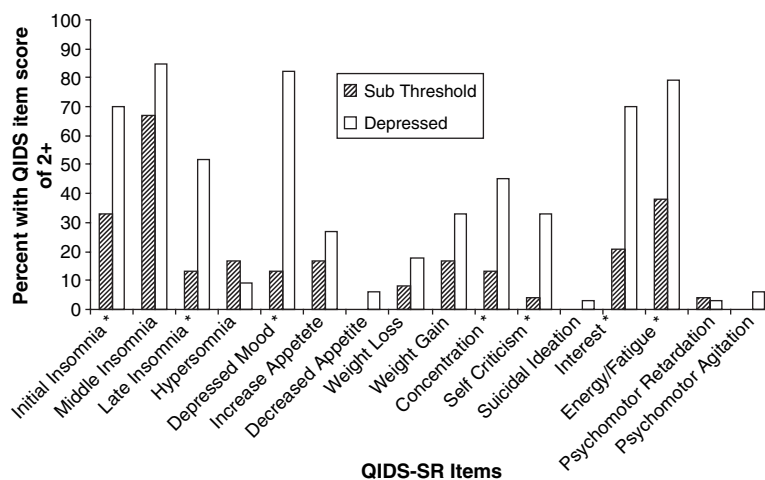


Figure 1. The Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) symptom profiles for the depressed and sub-threshold depression group. *Significant difference between groups.

disturbance, fatigue, and loss of energy [23]. The US Preventative Services Task Force recently recommended screening for depression, concluding that screening can improve outcomes [24,25]. Of the instruments available, questionnaires asking one question each about (1) depressed mood and (2) anhedonia appear to perform as well as longer instruments [24,26]. Furthermore, a recent analysis reports that good screening instruments for MDD make good severity instruments, with the advantage of decreased patient burden [27].

The novel combination of the PHQ-2 and QIDS-SR in this study has the advantage of using the former to screen for the presence of depression, while the QIDS-SR provides valuable information about specific symptoms endorsed in terms of severity, frequency and associated dysfunction. However, given our small sample size and lack of confirmatory diagnostic interview for MDD, larger studies are indicated to ascertain whether this screening process is an effective strategy in real world clinic settings.

In conclusion, the combined PHQ-2 and QIDS-SR can facilitate prompt detection of MDD as well as providing an easy-to-use measure to monitor specific symptoms and progress once treatment is initiated.

Key points

- Major depressive disorder affects one in every four patients with diabetes
- Studies show an association between depression and hyperglycemia, as well as impairment in disease self-management
- Depression often goes unrecognized in primary care and general hospital settings
- Combination screening strategies may facilitate prompt detection of depression as well as providing an ongoing measure to monitor specific symptoms

Acknowledgements

We are grateful to Anne Marie Jones, M.S., Ariell Flood, M.S., and Katrina Van deBruinhorst, M.A., who participated in screening patients for this study. Note, a brief description of the study and some of its findings were previously presented in a poster at the Future Leaders in Psychiatry Conference, 6 May 2006.

Statement of interest

Dr Daly has received an honorarium within the last year from the *Journal of Clinical Psychiatry* after participating in an Academic Highlights discussion regarding depression and physical illness. Dr Trivedi has been a consultant for Akzo (Organon Pharma-

ceuticals Inc.), Bristol-Myers Squibb, Cyberonics, Inc., Eli Lilly and Company, Forest Pharmaceuticals, Inc., Janssen Pharmaceutica Products, LP, Johnson & Johnson, Organon, Pfizer, Pharmacia & Upjohn, Sepracor, Solvay Pharmaceuticals, Inc., and Wyeth Pharmaceuticals. He has also received grant support from Abbott Laboratories, Inc., Akzo (Organon) Pharmaceuticals Inc., Bayer, Bristol-Myers Squibb, Cephalon, Inc. Corcept Therapeutics, Inc., Eli Lilly and Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Pharmaceutica, Johnson and Johnson PRD, Meade Johnson, the National Alliance for Research in Schizophrenia and Depression, the National Institute of Mental Health, Parke-Davis Pharmaceuticals, Pfizer, Inc., Pharmacia & Upjohn, Predix Pharmaceuticals, Solvay Pharmaceuticals, Inc., and Wyeth Pharmaceuticals. Dr Raskin has been a consultant for the following pharmaceutical companies within the last 3 years: Aventis Pharmaceuticals, Bristol-Myers Squibb Company, MannKind BioPharmaceuticals, Novartis Pharmaceuticals, Novo Nordisk and Takeda Pharmaceuticals. He has received grants from the following: the National Institute of Health-National Institute of Diabetes and Digestive and Kidney diseases, Glaxo Smith Kline, Eli Lilly, Novartis Pharmaceutical, Novo Nordisk and Takeda Pharmaceuticals and is the current editor of *The Journal of Diabetes and Its Complications*.

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ORIGINAL ARTICLE

Risperidone in adolescent schizophrenic psychoses: A retrospective study

MICHAL HRDLICKA & IVA DUDOVA

Department of Child Psychiatry, Charles University, 2nd Medical School, Prague, Czech Republic

Abstract

Objective. The aim of the study was to assess the therapeutic effect and tolerability of risperidone in patients with early-onset schizophrenia and other related psychotic disorders. **Methods.** Our retrospective study included 47 schizophrenic patients (27 boys, 20 girls) with an average age of 16.5 ± 1.3 years. The patients were evaluated based on their medical records prior to being started on risperidone, and then after 1, 3 and 6 weeks of risperidone administration. Efficacy of treatment was evaluated using the first item on the CGI scale. Survivors analysis was used. **Results.** After week 6, the average dose of risperidone was 3.8 ± 1.4 mg. Eighty-two percent of the patients were evaluated as responders, 64% as full responders and 18% as partial responders. There were eight patients who dropped out of the study during treatment. The initial inclusion score on the CGI was 5.8 ± 0.7 . This score showed a steady decrease at each evaluation point during the treatment. At week 1 the score was 4.5 ± 1.1 ($P < 0.001$), at week 3, 3.4 ± 1.2 ($P < 0.001$), and at week 6 it was 2.6 ± 1.2 ($P < 0.001$). The medication was well tolerated. Less than half of the patients (46%) reported any side effects, according to their medical records. Parkinsonism (19%), sedation (8.5%) and hypersalivation (8.5%) were the most commonly reported side effects. The mean weight of the participants increased from 61.2 ± 10.0 kg to 64.7 ± 10.0 kg between baseline and week 6 ($P = 0.002$). **Conclusion.** Our experience supports the use of risperidone in the treatment of schizophrenic disorders in adolescence.

Key Words: Schizophrenia, atypical antipsychotics, childhood, adolescence

Introduction

Atypical antipsychotics became an important part of modern psychiatric treatment during the 1990s and they have been successfully used in early onset schizophrenia. However, the literature on the use of atypical antipsychotics in pediatric patients remains limited. There are remarkably few randomized, controlled trials for adolescent schizophrenia [1].

The clinical trial experience with clozapine in adolescents with schizophrenia consists of one double-blind, short-term controlled study [2], three open-label studies [3–5] and one retrospective analysis of long-term treatment [6]. In the only randomized double-blind study, 21 treatment-resistant children and adolescents were treated with clozapine and haloperidol [2]. Clozapine was superior to haloperidol on all measures of psychosis and reduced both positive and negative symptoms. Clozapine produced more drowsiness and salivation, whereas haloperidol caused more insomnia. No cases of agranulocytosis were observed, but five patients

developed neutropenia, and three patients EEG abnormalities while on clozapine. One-third of the clozapine group had to be discontinued due to adverse effects.

Published data on risperidone consists of the introductory case study [7], four open-label studies [8–11] and one retrospective study [12]. The response rate in patients treated with risperidone in the open-label studies ranged from 60 to 91%. Extrapyramidal reactions, somnolence and weight gain were the most commonly reported side effects.

The pediatric experience with olanzapine includes several small, open-label studies [13–17] as well as two retrospective studies [18,19]. The response rate of non-resistant patients on olanzapine was reported to be in the range of 62–100%. Increased appetite, weight gain and sedation were the most frequently reported side effects.

Two open-label studies with quetiapine, in heterogeneous populations of patients with schizophrenia (schizoaffective disorder, bipolar disorder, psychotic depression, or psychosis not otherwise specified),

have been published [20,21]. Improvement over baseline was reported in both of the studies. Adverse effects included somnolence, headache, postural tachycardia, and weight gain.

There were two studies comparing risperidone and olanzapine with haloperidol, a typical neuroleptic drug. The first study was an 8-week controlled, double-blind trial carried out in 50 children and adolescents with schizophrenia or other psychotic illnesses [22]. At the endpoint, 74% of patients in the risperidone group, 88% in the olanzapine group and 53% in the haloperidol group had achieved significant improvement. Exploratory comparisons indicate that the magnitude of the antipsychotic response with atypical agents was comparable to that observed with haloperidol. Common side effects, somnolence, extrapyramidal side effects, and weight gain, occurred in all three treatment groups. The second study was an 8-week, open-label study that included 43 patients. In this study, all three medications appeared to be equally effective [23]. With regard to side effects, olanzapine and haloperidol induced fatigability more often than did risperidone, while haloperidol was associated with a higher frequency of depression and more severe extrapyramidal symptoms.

Armenteros and Davies [24] performed a meta-analysis of studies of antipsychotics on early onset schizophrenia. The average response rate for the eight studies employing atypical antipsychotics was 55.7% compared with 72.3% for the 13 studies employing typical antipsychotics. This difference was significant at the trend level ($P < 0.10$). Average weight gain in patients treated with typical antipsychotics was 1.4 kg, compared to 4.5 kg for those treated with atypical antipsychotics. Surprisingly, the rate of extrapyramidal side effects was similar between the two groups. This contradicted previous observation that had been in favor of atypical neuroleptics [25].

Based on a Medline search (July 2006), we did not find any reports describing treatment with ziprasidone, zotepine, or aripiprazole in early onset schizophrenia.

Methods

This was a systematic chart review of all patients receiving routine clinical care at the Department of Child Psychiatry who were being treated with risperidone for schizophrenia or related psychotic disorders between 1997 and 2001. These patients received a 2-h intake diagnostic and treatment evaluation by a child psychiatrist. All diagnoses were made by a treating child psychiatrist using ICD-10 criteria [26] based on interviews with the parent(s) and child and after review of available school and psychological testing reports. No formal structured interview was used. Since risperidone had

been registered in the Czech Republic for the treatment of schizophrenia in patients aged 15 years and older, an informed consent for "off-label use" was obtained from the parents of participants younger than 15 years of age.

Records of the patients were examined to ascertain the psychiatric diagnosis, concurrent psychiatric or somatic diagnoses, weight, prior medication trials including evaluation of treatment-resistance, concomitant medication, dose and length of treatment, and response to risperidone. Inclusion criteria were: (1) schizophrenia diagnosis of F20–29, (2) medical record quality sufficient to evaluate the patient, and (3) initiation of the risperidone treatment only after admission to the Department of Child Psychiatry, i.e. not used in out-patient care prior to the admission). A history of treatment-resistance was defined as a failure of two antipsychotic medications which had been administered over a period of at least 3 weeks.

One of the authors (I.D.), who had not been one of the treating physicians in any of the cases, served as an independent reviewer of clinical notes, to determine the effect of risperidone treatment on each of the patient's schizophrenic symptoms. The patients were evaluated based to their medical records prior to starting risperidone and then after weeks 1, 3 and 6 of risperidone treatment. The overall severity of the schizophrenic symptoms was assessed using the Clinical Global Impression (CGI) scale [27]. The CGI has been extensively used in psychopharmacology research on adults and juveniles and has been shown to be medication sensitive. The study used the first item on the scale (CGI – Severity) which ranges from 1 (not ill) to 7 (extremely ill). To determine the response to risperidone, the baseline CGI Severity score was compared to the scores at weeks 1, 3, and 6. We also made an endpoint evaluation (at week 6 or at discharge) regarding the general success of the treatment regimen. A global assessment of (1) effective, (2) partially effective, or (3) not effective, was determined for each participant.

Two other facets were also measured, these included: frequency of risperidone augmentation with other antipsychotic drugs and the frequency of use of acute sedative medication in cases of agitation. Adverse experiences associated with the medication, including the use of anticholinergic drugs, were also recorded.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 10.0). Descriptive statistics for the sample description was used. Changes in the first item of the CGI scale (CGI—Severity) and weight were analyzed using the paired *T*-test (baseline vs. risperidone treatment at weeks 1, 3, and 6). The McNemar test was used for the analysis of risperidone augmentation, use of acute sedative medication and for

anticholinergic drug use. Survivors analysis was performed.

Results

Description of the sample

In the period between 1997 and 2001, 66 patients were treated with risperidone for a schizophrenia diagnosis of F20–29 in the Department of Child Psychiatry. Of this number, 16 patients had been started on risperidone prior to admission and as such did not meet criteria 3, while in another three patients the quality of medical records was not considered satisfactory for the study and therefore failed to meet criteria 2.

The remaining 47 patients (27 boys, 20 girls) met all the inclusion criteria for the study. The mean age of the sample was 16.5 ± 1.3 years (ages ranged from 13–19 years). Twenty-five patients (53%) had schizophrenia, eight patients (17%) had schizoaffective disorder, and 14 patients (30%) had other schizophrenic disorders. For a more detailed description of the diagnoses see Table I. It was the first episode of illness for 32 patients (68%), 15 patients (32%) suffered from relapse. It was also the first psychiatric hospitalisation for 30 patients (65%), 16 patients (32%) had been hospitalized before, and in one case the information was missing. Six patients also had a concurrent somatic diagnosis: there were two cases of juvenile hypertension and one case each of asthma, multinodular goiter, hypothyroidism, and dyspeptic syndrome.

Twenty-five patients received psychopharmacological treatment prior to the admission. Antipsychotics were the most used psychotropic drugs: haloperidol (six cases); thioridazine (four cases); perphenazine and olanzapine (three cases); chlorpromazine, levomepromazine, chlorprothixene, and sulpiride (two cases); and trifluoperazine, tiapride,

pimozide, and flufenazine depot (one case each). The use of antidepressants was less frequent. Fluvoxamine, sertraline, fluoxetine, moclobemide and amitriptyline were used each in one case, whereas only clomipramine and dosulepin were used twice. Benzodiazepines (clonazepam, bromazepam) and mood stabilizers (carbamazepine) were given exceptionally. Forty-two patients (89.5%) were evaluated as treatment-non-resistant, three patients (6.5%) as treatment-resistant, and in two patients (4%) sufficient information was not available.

Twenty-one patients did not complete the 6-week hospitalization treatment period. Thirteen patients were discharged sooner, because of an excellent therapeutic response. There were eight drop-outs: five patients for lack of therapeutic effect, one patient for an acute dysphagic reaction, one patient for severe parkinsonism, and one patient for hypersalivation.

The mean daily dose of risperidone was 3.2 ± 1.1 mg at the end of week 1 (range 1.5–6.0 mg), 4.1 ± 1.4 mg at the end of week 3 (range 2.5–8.0 mg), and 3.8 ± 1.4 mg at the end of week 6 (range 1.0–6.0 mg).

Treatment efficacy

In the global assessment of the treatment, 44 patients were evaluated. This number includes five drop-outs which were due to lack of efficacy but excludes three drop outs that were due to severe adverse events. Thirty-six patients (82%) were rated as responders: 28 patients (64%) as full responders, eight patients (18%) as partial responders. Eight patients (18%) were evaluated as non-responders to the treatment.

The inclusion score on the CGI was 5.8 ± 0.7 and decreased significantly during treatment with risperidone (Figure 1). Augmentation of risperidone with other antipsychotic drugs was needed in 10 patients during week 1, in five patients during week 3, and in only one patient during week 6. Levomepromazine

Table I. Diagnoses of patients included in the study.

Diagnosis	No. of patients
Paranoid schizophrenia	13
Hebephrenic schizophrenia	2
Catatonic schizophrenia	1
Undifferentiated schizophrenia	4
Simple schizophrenia	1
Other schizophrenia	2
Schizophrenia, unspecified	2
Acute polymorphic psychotic disorder without symptoms of schizophrenia	2
Acute polymorphic psychotic disorder with symptoms of schizophrenia	2
Acute schizophrenia-like psychotic disorder	10
Schizoaffective disorder, manic type	3
Schizoaffective disorder, depressive type	2
Schizoaffective disorder, mixed type	3
Total	47

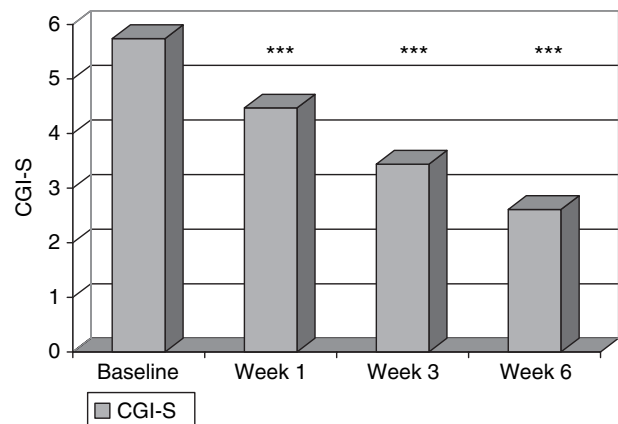


Figure 1. Improvement of CGI-Severity scores during risperidone treatment. Week 1 vs. baseline: $t = 8.445$; $df = 46$; Week 3 vs. baseline: $t = 11.588$; $df = 38$; Week 6 vs. baseline: $t = 11.387$; $df = 25$; *** $P < 0.001$.

was the most frequently used drug for augmentation (six cases), followed by haloperidol, thioridazine, sulpiride, pimozide, and zuclopenthixol. This decreased need for augmentation between week 1 and week 6 did not reach statistical significance ($P=0.375$). The need for acute use of sedative medication in cases of agitation was present in 15 patients at baseline; in six patients at week 1 ($P=0.004$ vs. baseline), in four patients at week 3 ($P=0.070$ vs. baseline), and in three patients at week 6 ($P=0.375$ vs. baseline). The decrease was statistically significant only at week 1, and this might be due to the decreasing number of patients in the sample over the time period of the study, e.g., early discharge of patients with an excellent response or drop outs.

Side effects

Less than one half of the patients (22 patients, 46%) reported any side effect according to their medical records. Sixteen patients, out of the initial 47 (34% of the sample) suffered from extrapyramidal side effects. The most common adverse events were: parkinsonism (19%), sedation (8.5%) and hypersalivation (8.5%). For a more detailed description of side effects, see Table II. No serious complications of the treatment program were observed.

Anticholinergic drugs were being used in 13 patients at baseline, in six patients at weeks 1 and 3, and in seven patients at week 6. This decrease in the use of anticholinergics during risperidone treatment did not reach statistical significance ($P=0.09$).

The mean weight for the group was 61.2 ± 10.0 kg at baseline, 61.7 ± 9.8 kg at week 1 ($t=1.761$; $df=41$; $P=0.086$; compared to baseline), 63.6 ± 9.4 kg at week 3 ($t=3.226$; $df=31$; $P=0.003$; compared to baseline), and 64.7 ± 10.0 kg at week 6 ($t=3.674$; $df=20$; $P=0.002$; compared to baseline). The average weight increase between baseline and week 6 was 3.5 kg.

Discussion

The response rate in our sample of patients reached 82%. This is comparable to some open-label studies with risperidone in adolescent schizophrenia where the response rate was 75%, as in the Drtilkova study [10] and 74% in the Sikich et al. study [22]. The response rate was almost the same as that described for risperidone in the RODOS study (84%). The RODOS study represents the largest retrospective study done with risperidone and olanzapine, with an adult population consisting of 1901 patients [28,29]. However, it is also well known that the response rates in retrospective and open-label studies are usually higher than in randomized, controlled, double-blind studies.

Table II. Adverse events in patients during risperidone treatment.

Adverse event	No. of patients	Percentage
Parkinsonism	9	19%
Sedation	4	8.5%
Hypersalivation	4	8.5%
Acute dystonia	2	4%
Akathisia	2	4%
Galactorrhoea	2	4%
Perioral dyskinesia	1	2%
Tremor	1	2%
Increased appetite	1	2%
Acute dysphagic reaction	1	2%
Gastrointestinal complaints	1	2%
Hypotension	1	2%

The mean daily dose of risperidone was 3.8 mg at the endpoint of our study compared to 6.6 mg daily at the week 6 endpoint in the Armenteros et al. [8] study. This reflects the current general tendency to use lower doses of risperidone than were used when risperidone therapy was initially tested. Sixty per cent of patients in the Armenteros et al. study [8] suffered from extrapyramidal side effects in contrast to 34% of the patients in our study. However, the sensitivity of the adolescent population to neuroleptic side effects, generally, seems to be higher than in the adult population. Forty-six percent of our patients reported any side effect according to their medical records whereas in the RODOS study it was only 13% [28]. The mean daily dose of risperidone in RODOS study through the treatment was 5.3 mg [29].

The retrospective design of our study did not allow us to analyse directly the relationship between the dose of risperidone and frequency of extrapyramidal side effects as no fixed dosing schedule and no formal rating scale for extrapyramidal side effects were used. Only indirect observation, expressed by the use of anticholinergics, was possible. However, changes in the use of anticholinergics during risperidone treatment were not significant.

Weight gain is one of the major concerns associated with therapy using atypical antipsychotics. The average weight gain described in our study was 3.5 kg over 6 weeks of treatment. This is similar to the Sikich et al. study [22] where the average weight gain in risperidone treatment group was 4.6 kg over 8 weeks of treatment. Other studies with risperidone have not reported the average weight gain for the whole sample, instead, only reporting the weight gain for patients who experienced a considerable weight increase [8,11]; consequently, the data are not comparable. Comparing our data with the data for olanzapine, we see considerable variation in weight gains. There were two olanzapine studies showing similar weight gains – 3.4 kg over 6 weeks [13], 3.8 kg over 6 weeks [17] – but there was also one study with a 7.1-kg increase over 8 weeks of treatment [22].

Our results show the efficacy and safety of risperidone in the treatment of adolescent schizophrenia and other schizophrenic psychoses and support its use for this indication. The safety and tolerability of risperidone in other pedopsychiatric disorders has already been demonstrated. Large randomized, controlled, double-blind studies with risperidone in disruptive behavior disorders [30–32] as well as in childhood autism and other pervasive developmental disorders [33,34] have been recently published.

The limitations of our study were its retrospective design, absence of a control group and relatively small sample size. Double-blind, randomized, placebo-controlled studies using risperidone for early-onset schizophrenia are needed to better determine efficacy, optimal dosing, safety and tolerability in this population.

Key points

- Atypical antipsychotics have been successfully used in early onset schizophrenia
- Risperidone in doses between 2 and 6 mg has been found to be an effective and safe treatment for schizophrenia and other related psychotic disorders in adolescence
- The sensitivity of the adolescent population to the side effects seems, generally, to be higher than in the adult population. Extrapyramidal side effects and weight gain were major issues that we wanted to evaluate in our study.

Statement of interest

The study was partly supported by Janssen-Cilag Czech Republic.

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ORIGINAL ARTICLE

Pilot of group intervention for bipolar disorder

DAVID CASTLE¹, MICHAEL BERK², LESLEY BERK³, SUE LAUDER³,
JAMES CHAMBERLAIN³ & MONICA GILBERT³

¹St Vincent's Hospital, Mental Health Research Institute, University of Melbourne, Melbourne, Australia, ²Barwon Health, The Geelong Clinic, University of Melbourne, Orygen Youth Health, Mental Health Research Institute, Melbourne, Australia, and ³Mental Health Research Institute, Parkville, Victoria, Australia

Abstract

Objective. This pilot study aimed to determine whether a group based psychosocial intervention reduced rates of relapse, improved function and quality of life in people with bipolar disorder. **Method.** Patients with a diagnosis of bipolar disorder, types I and II were recruited in the Geelong Region of Victoria. Patients were assessed at baseline for psychiatric status, mood episode, function, and medication adherence. They were randomly assigned to either the intervention arm, a 12-week, structured group-based therapy as an adjunct to treatment as usual or the control arm, which consisted of treatment as usual, plus weekly phone calls. Participants were then followed up for a period of 3 months and assessed by a researcher blinded to treatment and control interventions. **Results.** Functioning as measured by the Global Assessment of Functioning (GAF) was significantly improved in the intervention group ($P=0.008$). The social relationships subscale on the (WHOQoL-BREF) showed significant results ($P<0.05$ level). There was also a positive trend in reduction of relapses in the intervention group. **Conclusion.** The use of a group intervention for bipolar disorder as an adjunct to usual treatment has potential benefits, both in reduction of relapse and improvement in functionality, and may be a cost effective way of delivering psychosocial treatments.

Key Words: Bipolar disorder, group, psychosocial, relapse, functionality

Introduction

Bipolar disorder is common, occurring in at least 1% of the population. The World Health Organisation ranks it as the sixth most disabling condition across physical and psychiatric disorders [1]. Bipolar disorder is also the most lethal psychiatric disorder, with high rates of suicide [2]. It is commonly misdiagnosed, with delays to accurate diagnosis of over 10 years [2]. There is also a high incidence of co-morbidity (particularly with substance abuse, anxiety disorders, and personality disorders), which is associated with greater treatment complexity and poorer therapeutic outcomes [3].

Pharmacological agents play a primary role in mood stabilisation [4], but problems with adherence to medication clearly contribute to the efficacy–effectiveness gap of pharmacological treatment [5]. Furthermore, rates of relapse even while on mood stabilisers are noted to be as high as 40% in the first year, 60% in the second year and 73% over 5 or more years [6]. A recurring cycle emerges, indicating

the higher the number of previous episodes, the higher the possibility of relapse [7].

Psychosocial interventions combined with pharmacological treatment may have the potential to interrupt this cycle. Some interventions have focussed primarily on medication adherence. Scott and Pope [8] found that attitudes and beliefs about bipolar disorder were important predictors of adherence, and medication adherence has been targeted successfully in previous psychosocial interventions [9,10]. However, the benefits of psychosocial interventions have been suggested to “go beyond compliance enhancement” [11]. Studies have found that people with bipolar disorder who are able to identify and respond to prodromes, especially prodromes of mania, show improved outcomes [12]. In bipolar disorder, malleable vulnerabilities include sensitivity to circadian rhythm disruption, negative and positive life stressors, levels of expressed emotion and negative affective style in the family, and dysfunctional cognitive styles and schemas [13].

While effectiveness of the varied psychological interventions has yielded encouraging results, there is no definitive evidence regarding the superiority of any particular therapy [14]. In part this may be due to the overlapping elements of other paradigms evident in these interventions [15]. What appears to be most crucial in the efficacy of psychosocial interventions is that core components are addressed [14,16] and that this is done in a sequential and structured framework that gives focus to the development and enhancement of skills in an ongoing way [14]. These key aspects include psycho-education, compliance enhancement, early identification of prodromes, stresses, and lifestyle stability.

Where success has been shown with other interventions, sustainability, retention rates and cost-effectiveness may prove to be issues in their broader application within naturalistic settings (e.g., [11,17]). While group interventions have a greater cost effective advantage in general over individually based programs, a challenge for all interventions is the sustainability of improvement beyond the intervention. The development of skills such as cognitive restructuring, monitoring, stress reduction etc requires practice and reinforcement. To achieve this goal in a cost effective way, our group has incorporated as an integral part of the learning structure, an interactive journal, "The Collaborative Therapy Journal" (CTJ).

The CTJ is held by the individual and provides the opportunity for the individual to practice skills learned in the group setting. This is done between group sessions and as part of their long term maintenance, incorporating key partners, such as health professionals and family members.

It addresses three key areas in an individualised way that supports a person's recovery.

1. *Treatment participation* – for example, medication monitoring, side effects, education, self-efficacy. The CTJ as a collaborative tool between patient and service provider may be an additional way of realising the integration of skills and information gained from a psychosocial intervention in real life settings [18]. This extends Essex et al.'s [19] approach of using shared record keeping to enhance long-term self-management of illness by including personalised information and coping skills.
2. *Syndromal recovery* – for example, symptom monitoring, relapse prevention plans, developing relapse signatures.
3. *Functional recovery* – for example, cognitive restructuring through identification of vulnerable situations and challenging associated negative thinking patterns and behaviours; and action plans.

Group therapy is seen to have added benefits to individual intervention, with the context of group

process encouraging social functioning and providing the buffering effects of social support [20,21]. It is also a model of treatment which already has a place within existing service delivery frameworks, at least in part due to issues of efficiency and practicality. Van Gent et al. [22], in a small randomised controlled study ($n=34$), confirmed the advantage of a few sessions of group psycho-education on self-confidence, behaviour and social functioning but not on symptom reduction. A second study [23] confirmed these findings and recorded an added advantage in thinking and behaviour as measured on a symptom checklist in the group receiving the extended psycho-education plus psychotherapy intervention (10–13 sessions). Colom et al. [11] published the only large group-based intervention for bipolar disorder that has employed a randomized controlled design. These authors' [11] 21-session group based psycho-education intervention also incorporated a number of key approaches of other interventions, including stress management techniques, problem-solving, establishment of routines and strategies for managing warning signs. In comparison with a befriending group (to control for the supportive effect of the group itself), the intervention group experienced a significant reduction in the number of participants who relapsed and number of recurrences per person. The number and length of hospitalizations were also lower for those in the intervention group.

The pilot study we report here evaluated the effectiveness of a "collaborative therapy management package" for people with bipolar disorder developed at the Mental Health Research Institute, Victoria. The specific aims were to reduce rates of relapse; improve global functioning and quality of life; and evaluate satisfaction with the format of the group as part of conducting a randomised control trial. We report on 6-month follow-up data and relapse data over 10 months.

Methods

Subjects

A total of 20 subjects were recruited in this pilot study. Inclusion criteria were: a current DSM-IV diagnosis of bipolar affective disorder with symptom severity that did not interfere with the ability to participate in a group for an estimated 1.5-h session; age 18 years or over; ability to converse in English without an interpreter; being under the care of a medical practitioner; and showing no evidence of an organic aetiology or significant developmental disability.

Potential subjects were referred by service providers at public and private treatment facilities, non-governmental organizations and by self-referral. All potential participants required a diagnosis of bipolar

disorder (according to DSM-IV criteria) to be confirmed by their treating doctor for entry to the trial. Following informed consent patients were assessed by one of the study Research Assistants (RAs), before being randomized to the experimental or control condition, using a computerized randomization system to ensure true randomization.

Study design

This was a randomised control trial comparing a group-based intervention (experimental) to treatment as usual (control).

Treatment

All patients included in the study were under the management of a medical practitioner (GP or psychiatrist). They received their usual pharmacological treatment and were not enrolled in any other structured group therapy programs.

Control condition (CP: Control-plus supportive phone calls)

The control condition consisted of treatment as usual, as described above, combined with weekly phone calls from the researchers to control for any extra contact time with researchers outside of the structured intervention group.

Experimental condition

The experimental condition consisted of treatment as usual plus a group therapy program delivered in an outpatient setting once a week for 90 min over a period of 12 weeks. In addition, three booster sessions were conducted at monthly intervals after conclusion of the 12-week program. The groups consisted of education, peer support, new coping strategies and the development and practicing of skills designed to enhance a person's ability to manage their mental health and to maintain wellness (i.e. relapse prevention). The group-based component included a manual to ensure treatment fidelity and provides a number of structured tools to reinforce and enhance skill development initiated within the group session. The groups were facilitated by two research assistants with demonstrated clinical experience and training in psychosocial interventions and group delivery (see Table I).

Tools of the group

The group intervention included a participant workbook for patients to note personal information such as prodromes, goals, and brainstorm information and to practice skills such as problem solving. An information book was also provided. This gave

Table I. Content of group therapy sessions.

Session 1	Introduction to group and bipolar illness
Session 2	Stress and triggers associated with bipolar disorder
Session 3	Monitoring of stress/triggers
Session 4	Assessment of stressors and coping skills
Session 5	Preventing relapse via problem solving, stress tolerance and goal setting
Session 6	Medication management
Session 7	Managing and monitoring prodromes of depression
Session 8	Assessment of prodromes of depression and helpful activity skills
Session 9	Preventing relapse: developing relapse prevention plans for depression
Session 10	Managing and monitoring prodromes of mania/hypomania
Session 11	Assessment of prodromes of manic/hypomania and cognitive skills
Session 12	Preventing relapse: relapse prevention plans for mania/hypomania
Booster 1	Review of skills and supports including relapse plans
Booster 2	Problem solving skill integration
Booster 3	Consolidating skills into daily life

information that reinforced the psycho-education material covered in the group. Each participant also utilizes a Collaborative Therapy Journal (CTJ), a pocket sized journal with key personalized information such as charting of stressors, early warning signs, coping strategies and other factors that influence the course and management of a person's mental health. As part of the group process, patients were taught to use the CTJ and encouraged to use it in conjunction with their regular service providers.

Weekly follow-up phone checks were made over the duration of the group intervention to remind treatment participants of the next group session, and to offer support for any homework tasks assigned. Weekly phone calls to the control group over this period controlled for any extra contact time with researchers outside of the structured intervention group.

Assessment procedures and instruments

Patients were assessed at baseline and 6 months regarding psychiatric status, relapse rates, social functioning, quality of life and level of functioning. Trained Research assistants "blind" to whether the individual received the intervention or control condition performed all assessments excluding the GAF where raters (Research Assistants) who had more extensive knowledge of the patient's social, occupational and psychological functioning were used. These raters were blind to earlier GAF scores.

Quantitative instruments and assessment protocol

Demographic data included age, sex, marital and employment status. The Mini International Neuropsychiatric Interview (MINI) [24] was used

as a structured interview to ascertain primary and comorbid DSM or ICD diagnoses, and in particular to classify the sample into type of illness (Bipolar I or II).

Symptom measures included: the Montgomery and Asberg Depression Rating Scale (MADRS) [25] for depressive symptoms and the Young Mania Scale (YMRS) [26] for manic symptoms; the Global Assessment of Function scale (GAF) [27] measures level of function; and the WHOQoLBREF [28] assesses quality of life. Medication adherence was assessed using the Medication Adherence Rating Scale (MARS) [29].

Definition of relapse

Participants were considered to have “relapsed” if they met the DSM-IV criteria for a manic or depressive episode, and/or required hospital admission.

Statistical methods

Two methods were used to analyse the outcome measures in the quantitative instruments: ANCOVA and ordinal logistic regression. In both cases the dependent variable was the outcome measure at 6 months and the two explanatory variables were the measure at baseline and the variable indicating treatment or control. These analyses take into account the differences between treatment and control at baseline as well as investigating any treatment effect.

In the analysis of the outcome measures, P values were adjusted using Bonferroni correction for multiple tests (10 in total) as well as unadjusted P values.

Results

Retention

From an initial sample of 20, two patients withdrew prior to the commencement of the intervention, one due to study commitments and another through disappointment at being randomised to the control condition. One patient failed to meet criteria for euthymia necessary for initial trial participation. Once the intervention commenced, there were no withdrawals, providing an overall retention rate of 90%. Based on t -tests, Mann-Whitney and χ^2 -tests and using $\alpha=0.05$, there were no significant differences at baseline between the control and treatment groups for the 10 items comprising the quantitative instruments (see Table III). Note that while there is a difference on the MADRS of 6 between the baseline, treatment and control mean scores this was not significant at $\alpha=.05$ because of the large standard deviations.

Baseline characteristics of the groups

The mean age of the 17 participants in the pilot was 44 (standard deviation 10), with three males and 14 females. Eleven subjects were married, three had a partner but were not married, one was separated and two were divorced. Ten subjects had a diagnosis of Bipolar I and seven had a diagnosis of Bipolar II. Nine subjects were unemployed, seven had part-time work and one had full time work. Further details are shown in Table II. Fisher's exact test on these baseline characteristics gave no significant differences between the control and treatment groups.

Two measures, the GAF and the social relationships subscale of the WHOQoL-BREF, gave significance at the $\alpha=0.05$ level (unadjusted). For the ANCOVA analysis of the GAF the P value for the treatment effect was 0.008 (adjusted $P=0.08$) with the mean improvement due to treatment equal to 12 with confidence interval (3–21). Note that the full range for the GAF is between 1 and 100. The corresponding analysis with the ordinal logistic regression gave $P=0.012$ (unadjusted) and $P=0.12$ (adjusted) for the treatment effect. The P value for the interaction between treatment and baseline score for WHOQoL-BREF social relationships subscale was 0.008 (adjusted value 0.08). At 6 months, the individual scores for the control group were close to the corresponding baseline scores. In contrast, the three subjects in the treatment group who had low baseline scores (less than 50) improved by an average of 36 (SD 20). This is reflected in the means and standard deviations of the change scores for this measure as detailed in Table III.

Relapse data were collected for nine control subjects and eight treatment subjects over 10 months. Four control subjects experienced relapse, whereas there was only one relapse in the treatment group, but this was not statistically significant ($P=0.3$). The

Table II. Characteristics of study participants.

	Control	Treatment	Total
Age in years, mean (SD)	44 (8)	44 (13)	44 (10)
Sex:			
Male	2	1	3
Female	7	7	14
Diagnostic Subtype:			
Bipolar I	2	3	5
Bipolar I – with psychotic features	2	3	5
Bipolar II	4	3	7
Marital status:			
Married	6	5	11
With partner	1	2	3
Divorced	2	0	2
Separated	0	1	1
Usual medical practitioner:			
Psychiatrist	7	6	13
GP	2	2	4

Table III. Means and standard deviations of outcome measures.

Measure	Control		Treatment		Change score*	
	Baseline	6 months	Baseline	6 months	Control	Treatment
MADRS	6.0 (7.0)	5.8 (8.0)	12.1 (8.7)	13.0 (7.3)	0.2 (6.2)	-0.9 (10.5)
MRS	3.8 (3.4)	3.5 (6.4)	5.8 (7.2)	5.3 (5.2)	0.3 (4.1)	0.5 (10.4)
MARS	7.1 (2.7)	7.6 (2.4)	7.3 (2.1)	6.9 (2.7)	0.4 (1.7)	-0.4 (2.0)
GAF	61 (10)	62 (9)	56 (12)	72 (11)	1 (8)	15 (11)
WHOQoL:						
Quality of life	3.7 (0.5)	4.2 (0.7)	4.1 (0.8)	3.8 (0.9)	0.6 (0.5)	-0.4 (0.9)
Satisfaction with health	3.6 (0.9)	3.8 (0.4)	3.6 (1.3)	3.8 (0.7)	0.2 (0.8)	0.1 (1.1)
Physical health	68 (13)	69 (15)	60 (13)	66 (13)	0.4 (14)	7 (9)
Psychological health	57 (17)	60 (17)	56 (17)	58 (19)	3 (12)	2 (14)
Social relationships	68 (19)	66 (21)	52 (28)	60 (14)	-2 (9)	8 (30)
Environment	68 (19)	71 (15)	80 (10)	80 (13)	2 (14)	0.8 (9)

*Positive indicates improvement.

proportion of subjects having one or more relapses was analysed using Fisher's exact test, giving a *P* value of 0.3 (see Table IV).

While most subjects had zero or one relapse, two subjects each had two relapses in the 10 months. Consequently, the number of relapses for each subject was analysed using a Mann-Whitney rank sum test, giving $z = -1.5$ (negative due to fewer relapses in the treatment group) (*P* value of 0.14).

Discussion

The objective of this pilot was to determine the feasibility of a group-based intervention for people with a diagnosis of bipolar affective disorder in reducing relapse and improving functionality. Preliminary data on two key measures, numbers of relapse and global assessment of function suggest that the use of this type of intervention has merit as an adjunctive therapy to usual treatment. GAF scores showed a significant improvement in global functioning. This early finding provides some cautious optimism that such interventions may assist in reducing the impairment that is seen in this disorder. Future studies which focus on specific aspects of functional indicators could also further enhance our understanding by exploring individual functional indicators to identify if there are particular areas that are more amenable to the intervention.

The interaction result on the WHOQOL indicates that low scores on the social relationship subscale are more likely to improve in the intervention group than the control group. It may be that the collaborative process of relapse prevention plans and the group process, itself, played some role in this. In

addition, some of the skills covered in the manual, for example, problem solving may have been applied to social relationships. Larger samples and an active control group (e.g., befriending), would be needed to further examine this finding.

A strength of this pilot study was the application of a group-based format and the incorporation of the CTJ. There have been few such studies undertaken using a group format, almost all the trials in the literature being individual based. The manualised nature of the intervention enhanced fidelity, which may again facilitate its broader utility.

A potential weakness of the study is the lack of an active intervention for the control group. Befriending groups have been noted by some authors to be a useful control condition as it removes therapist contact as a variable between the intervention group and the control group [30]. It also provides some control for the effects of being in a supportive group environment. It is implicit in the nature of pilot data that the sample size needs to and will be increased. Trends, such as lower relapse rates that are non-significant in this report may become significant.

This model attempts to select out the key psychotherapeutic "active ingredients" from the published literature, and incorporate them into a manualised group-based format designed for simplicity of roll out. It is augmented by the use of self-efficacy and self-monitoring and action plans, in the form of the hand held Collaborative Therapy Journal. The results of this pilot study suggest that this model may have utility in naturalistic settings. It is planned to further develop the model and increase the sample size to one which will be powered to detect meaningful differences.

Key points

- A psychosocial group based intervention for bipolar disorder was delivered as an adjunct to treatment as usual

Table IV. Analysis of relapse.

	Treatment	Control	Total
One or more relapses	1	4	5
No relapse	7	5	12
Total	8	9	17

- A collaborative approach to minimize relapse and enhance functioning
- Improvements in functionality with a psycho-social intervention were enhanced
- Integrating psychosocial and pharmacological treatment has potential benefits for people with bipolar disorder

Statement of interest

This study was supported by funding from beyond-blue, Eli Lilly and the Medical Benefits Fund.

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CASE REPORT

Topiramate-induced psychotic exacerbation: case report and review of literature

ERSİN HATİCE KARSLIOĞLU¹, HANDE KARAKILIÇ², ENDER TANER³ & BEHÇET COŞAR³

¹Psychiatry Clinic, Ankara Oncology Training and Research Hospital, Ankara, Turkey, ²Ministry of Interior, General Directorate of Security, Turkish National Police Organization, Department of Health Services, Centre of Mental Health, Ankara, and ³Department of Psychiatry, Gazi University School of Medicine, Turkey

Abstract

Background. Topiramate (TPM) is a new antiepileptic drug that is used mainly in the treatment of refractory partial epileptic seizures. There are some studies reporting TPM's effectiveness in the treatment and maintenance of some psychiatric illnesses such as acute mania, some other affective disorders, post-traumatic stress disorder and binge-eating disorder. On the other hand, it has been shown that TPM may cause mild to moderate cognitive impairment and is thought to be responsible for a series of neuro-psychiatric signs and symptoms. Some of the available articles that have mentioned the relationship of psychotic symptoms and topiramate usage are discussed. **Objective.** The present paper aims to discuss a case of psychotic exacerbation purported to occur after TPM administration and to review specifically the literature on TPM's potential for inducing psychotic symptoms. The patient presented here is thought to be an undiagnosed schizophrenia patient until his admission to our clinic (Department of Psychiatry, Gazi University Medical School) with TPM-exacerbated psychotic symptoms. **Conclusions.** The current findings are still subject to controversy because of the presence of both individual case reports and case series on the association between appearance of psychotic symptoms and TPM usage.

Key Words: Topiramate (TPM), schizophrenia, psychiatric adverse effects, induced psychosis

Introduction

Topiramate (TPM) is a highly efficient new anti-epileptic drug that is used as an enhancing agent in the treatment of refractory partial epileptic seizures [1,2]. TPM exert its antiepileptic action through many mechanisms, it antagonises the neurotransmitter glutamate at the AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate receptors and potentiates the effect of the neurotransmitter GABA (γ -aminobutyric acid). It, also inhibits neuronal state-dependent sodium channels and carbonic anhydrase isoenzymes II and IV [1,3]. In addition, it is claimed that TPM may have antipsychotic effects mediated through its glutamate antagonism [4–6]. There are studies reporting TPM's effectiveness in the maintenance treatment of acute mania and other affective disorders [7–9], in the treatment of posttraumatic stress disorder and binge-eating disorder and in migraine prophylaxis [4,10–12], while there are case reports of trials of TPM for the purpose of weight reduction in patients

having gained weight secondary to antipsychotic use [13,14].

TPM may cause mild to moderate cognitive impairment. TPM is also thought to be responsible for a series of neuropsychiatric signs and symptoms, such as headache, dizziness, fatigue, weakness, ataxia, confusion, speech disturbances, delayed response, disturbances of memory and sleep, crying spells and depression. However, these symptoms usually recede upon cessation of TPM [15,16]. A limited number of case series report psychotic symptom development related to TPM use [15–19].

The present report aims to discuss a case of psychotic exacerbation purported to occur after TPM administration and to review specifically the literature on TPM's potential for inducing psychotic effects.

Case presentation

In October 2003, a 37-year-old married, college-educated government official, applied for the first

time to the out-patient unit of the Psychiatry Clinic, Gazi University Medical Faculty Hospital, upon his family's coercion. He had no history of previous psychiatric treatment. His main complaints were loss of the sensation of taste, inability to draw pleasure from anything and forgetfulness. Since the previous year he had been followed with a diagnosis of "hereditary spastic paraplegia" at the Neurology Clinic of another hospital. His therapeutic regimen first consisted of only 4 mg/day dantrolene, p.o., which was later modified in April 2003 with the addition of 100 mg/day TPM, p.o., for "peripheral neuropathy". The psychiatric complaints – which the patient identified as side-effects he attributed to TPM – began immediately after initiation of TPM treatment. The clinical symptoms were as follows: somatic complaints such as: his body was wasting away and would disappear, his penis and head were shrinking and his nails were becoming flattened. Besides, he had many bizarre thoughts such as: his body was emitting light and producing electricity and had special powers such as ability to absorb fats through his hands which enabled him to make people lose weight. He felt he had the ability to foresee the future and he believed that he could influence other people's brains, which happened under the influence of an "external power". He even thought of committing suicide to destroy "the power" in his struggle against it. Starting around September 2003, he became highly interested in mystic and religious subjects, and became extremely jealous. His functioning at work and interpersonal relations were diminished. His family reported increased irritability following TPM administration as well as bizarre laughter and hand and arm gestures.

The patient was hospitalized with a diagnosis of TPM-induced psychosis. During his sessions at the in-patient unit, his introversion and difficulty with finding words were noticeable. He had a cautious and distrustful countenance.

The clinical picture consisted of visual and auditory hallucinations, experiences of depersonalization and derealization, blocking of thought processes, impoverished content of thought, somatic and nihilistic delusions as well as delusions of grandeur, of jealousy, and of control. He displayed inappropriate and superficial affect and the prevailing mood was dysphoric and anxious.

Electroencephalography (EEG) and magnetic resonance imaging (MRI) findings were normal.

Premorbid characterization of the patient by his relatives was that of an introvert, suspicious man who did not converse much and who only ingested food the preparation of which he had seen. His aggressive demeanour had been present for the past 8 years. He had always complained of sleep disturbances: he used to say that he didn't go to sleep because he felt he would die. Four years

previously, he had inserted a glass in his anus as a result of which he had undergone a rectal operation. During the previous year he had behaved in a bizarre way, had sudden frights and startle reactions. His mystic tendencies and interest in religion, his belief in a "power" influencing him as well as his auditory hallucinations, predated the present presentation of the patient. When this information about the patient's premorbid status was integrated with the initial anamnestic information, according to DSM-IV criteria, the case was reformulated as "schizophrenia with TPM-induced psychotic exacerbation".

As there was no mention in the literature of psychosis related to dantrolene use and, following the opinion of the neurology consultant, it was decided that there was no need to discontinue dantrolene. So, only TPM was discontinued. For 1 week following TPM discontinuation, as no change was observed in the symptom profile, olanzapine treatment was initiated. The dose of olanzapine was started at 10 mg/day and titrated upwards to 30 mg/day. Symptoms such as auditory hallucinations, delusions and anxiety significantly improved in response to pharmacological treatment. Initial Brief Psychiatric Rating Scale (BPRS) score was 60 and it decreased to 45 at the end of 6 weeks of olanzapine treatment. The patient is now being regularly followed-up at the out-patient unit following his discharge from the hospital.

Discussion

In studies performed before TPM was approved for clinical use, the incidence of psychosis with TPM was found to be the same as that of placebo [15]. TPM-induced psychiatric adverse events in phase III double-blind placebo-controlled studies included depression, irritability, behavioral problems and lability of mood [20,21].

As clinical use of TPM became widespread, cases displaying symptoms that were thought to be associated with TPM were presented in case series or individual case reports.

While depression was observed in 25–65% of patients with treatment-refractory epilepsy [22,23], the incidence of psychotic disorders in these patients was 6–12 times greater than that in non-epileptic patients [24]. "Forced normalization" is a conceptualization to explain the development of psychiatric symptoms in epileptic patients [25]. This term covers the development of clinical behavioral anomalies in patients with previous EEG tracings demonstrating abnormal epileptiform activity and the normalization of findings in recent EEG tracings of the same patients [26,27]. This phenomenon should be considered in the assessment of epileptic patients.

Some authors claim that psychiatric adverse events (PAEs) develop preferentially in patients

Table I. Comparison of some psychiatric assessments before treatment and during follow-up.

	Before treatment	During follow-up (6th week)
Brief Psychiatric Rating Scale (BPRS)		
Schizophrenia	34	25
Depression	26	20
Total	60	45
Calgary Depression Scale for Schizophrenia (CDSS)	13	5
Scale for the Assessment of Negative Symptoms (SANS)	21	19
Scale for the Assessment of Positive Symptoms (SAPS)	5	5

who are initiated on pharmacotherapy at a later stage of their illness and at higher doses. They support this claim by the finding that patients who develop PAEs have longer periods of drug use than patients who discontinue the drug for some reason or another [23,28].

Cabeza et al.'s case report mentioned a patient who developed schizophreniform disorder following TPM treatment [19].

Khan et al. reported five cases with different combinations of sudden onset paranoid delusions, auditory hallucinations and depersonalization symptoms induced by TPM. They maintained that TPM-induced psychosis was completely reversible upon decrease in dose or drug discontinuation, and that it fully responded to appropriate antipsychotic treatment. In the same paper, although it was recommended that TPM administration be avoided in patients with a history of psychosis, still it was stated that similar adverse events may occur in patients without a history of psychiatric disorders [15]. Cognitive adverse events were not taken into account in this study. Three of the patients did not have a history of psychiatric disorders. Although the drug was slowly titrated upwards in all the patients, the time of onset of psychotic symptoms was variable. Symptoms rapidly resolved (within 24–48 h) when the drug was discontinued in one patient, when the dose was decreased in three patients and when an antipsychotic medication was added in one patient.

Trimble et al. examined vigabatrin-, TPM- and tiagabine-associated symptoms, which required immediate medical intervention and reported the development of affective disorders in 40 out of 89 patients (depression in 30 patients, affective psychosis in eight patients and hypomania in two patients). They also reported non-affective psychotic states such as schizophrenia-like paranoid states in 37 patients, organic delirium in 11 patients and one patient was left without any definitive diagnosis. The authors suggested that the development of psychosis was dose dependent. Interestingly, 15% of all psychotic patients had a history of psychiatric disorders. In the light of these data, they drew the conclusion that patients with a history of depression had a predisposition to develop affective disorders, while those with a history of psychosis were prone to develop psychotic symptoms. However, they emphasized the necessity of assessing possible drug inter-

actions since most of the patients were on polytherapy [29].

Aldenkamp et al. claimed that cognitive impairment associated with TPM use was less frequent than that seen to occur with valproate use. However, they also pointed out that TPM was responsible for impairment in short-term verbal memory tests [30]. Similarly, Reife et al. reported that TPM impaired cognitive functions, particularly those related to memory function [31].

When TPM was added to the treatment of a schizophrenia patient with persistent negative symptoms, improvement in these symptoms was observed in Drapalski's case report [32]. The studies of Deutsch et al. indicated improvement, particularly in negative symptoms, when the drug was very gradually titrated and a maximum dose of 100 mg/day was used [6]. Following these findings, it was suggested that TPM might be beneficial in targeting cognitive dysfunction and negative symptoms [5,6]. However, worsening of psychosis after replacement of adjunctive valproate with topiramate in a schizophrenic patient [33] makes this suggestion questionable. Besides, with respect to the present report, topiramate use in patients with schizophrenia should be handled with extreme caution.

As reported by Dursun and Deakin [34], lamotrigine, a glutamate excess release inhibitor, was found to be superior to topiramate in augmentation of clozapine resistant patients. Topiramate, besides being a glutamate antagonist at AMPA and kainate receptors also potentiates GABA function, which may decrease functioning of glutamate decarboxylase which converts glutamate to GABA further increasing the imbalance in glutamate levels. This may further increase the glutamatergic/GABAergic deficit in schizophrenia [35]. The clinical effect of topiramate in provoking psychosis may be due to its effects on the glutamate system.

Stella et al. reported two cases receiving TPM treatment for epilepsy who subsequently developed acute psychosis. The two cases had no history of psychiatric disorders. In one case, psychotic symptoms developed immediately after TPM dose was increased to 150 mg/day, while the other developed such symptoms with 1 day delay after the dose was increased to 350 mg/day. In both patients, in the first case a few days after the dose was decreased and in the second when the drug was discontinued,

symptoms resolved completely without any further need for antipsychotic treatment [16]. Verhoeven et al. reported three patients who developed psychotic symptoms following administration of TPM and whose symptoms disappeared completely upon drug discontinuation without any further need for antipsychotic treatment [17]. These authors suggested that visual/auditory hallucinations and delusions were the most common symptoms encountered in TPM-induced psychosis. Most of the studies [16,17] report spontaneous resolution of psychotic symptoms after discontinuation of topiramate; however, some other studies point out the necessity of using antipsychotic medication to clear symptoms of psychosis secondary to topiramate use [36] as in our case.

Millson et al. reported three schizophrenia patients on clozapine treatment whose illnesses exacerbated upon addition of TPM [37].

Although Kanner et al. reported PAEs in 13% and psychotic symptoms in 15% of 596 patients, in only 3.4% of these patients was it necessary to discontinue the drug due to these events. Noticeably, 26% of these had a past history of psychiatric disorders, hence the question arose whether these adverse events were associated with TPM use or whether these should be considered as recurrences of previous disorders [38].

There is only limited data in the literature on TPM administration for disorders other than epilepsy. There are reports of cognitive adverse events, whereas reports of PAEs are much less and this is assumed to be related to the administration of TPM at lower doses (100–200 mg/day) in these disorders [38].

Mula and Trimble conducted a study investigating psychopathology associated with TPM use. They evaluated 103 patients on TPM treatment for epilepsy who developed a psychiatric disorder. They reported affective disorders in 46, aggressive behavior in 22, psychoses in 16, anxiety disorders in 11 and personality changes (anger, agitation and hostility) in eight of these patients [39].

The same group of authors published another study investigating the occurrence of PAEs in epileptic patients on TPM therapy. A total of 431 patients were evaluated and psychotic disorders were observed in 16 of these. They drew the conclusion that PAEs were associated with high initial dose and rapid titration of the drug. In addition, they established that individual or family history of psychiatric disorders might be an important risk factor for the development of psychosis [40].

The patient presented here is thought to have been an undiagnosed schizophrenia patient until his admission to the Gazi University Psychiatry clinic with TPM-exacerbated psychotic symptoms. Exacerbation of psychosis in this patient occurred at relatively lower doses (100 mg/day) compared to similar

reports in literature (150–350 mg/day) [16]. Although the psychotic exacerbation was reported to occur at higher doses, as seen in this report it can happen even at low doses. In the light of present literature, we may presume an association between TPM use and exacerbation of both positive and negative symptoms and of cognitive impairment. Since a diagnosis of epilepsy was excluded as a result of appropriate clinical and laboratory evaluations, the episode of psychotic exacerbation cannot be explained by the concept of “forced normalization”. Although a diagnosis of “hereditary spastic paraplegia” could not be definitively confirmed, neurologists considering clinical findings to be consistent with the diagnosis, recommended continuation of dantrolene administration. Since there is no known reported pathogenic association between “hereditary spastic paraplegia” and schizophrenia in the prevailing literature, the two processes were interpreted as separate and coincidental entities. However, it is not possible to exclude the possibility that having received a diagnosis of “hereditary spastic paraplegia” might have acted as a precipitating stressor contributing to worsening of psychotic symptoms. The present case’s psychotic symptoms are considered to be associated with TPM use principally because of a close temporal relationship between significant worsening of symptoms and initiation of TPM treatment.

In the literature at large, studies indicate that TPM might potentiate antipsychotic activity and contribute to improvement in negative symptoms and cognitive deficits in schizophrenia patients. This is at least theoretically supported by the glutamate-mediated neuronal toxicity hypothesis. It is hypothesized that disinhibition of glutamate release at the AMPA/kainate receptors may result in excitotoxic neuronal injury. This progressive neuronal injury may in turn be responsible for findings such as ventricular enlargement and psychosocial deterioration in at least a subgroup of schizophrenia patients [41]. NMDA receptor hypofunction and increased and irregular AMPA/kainate receptor stimulation are well-documented phenomena in schizophrenia. Therefore it is inferred that TPM antagonism at the AMPA/kainate receptor may particularly improve negative symptoms [41]. As a clinical illustration, Drapalski reports a case of TPM addition to the treatment of a schizophrenia patient which led to improvement in negative symptoms [32].

However, the findings in this direction are subject to controversy because of the presence of both individual case reports and case series on the association between appearance of psychotic symptoms and TPM use. The present case report is also along the same vein. Case reports in general emphasize TPM-associated increase in parameters such as positive symptoms, cognitive deficits, depression, hostility and aggression.

In conclusion, clinicians are strongly advised to request detailed individual as well as familial history of psychiatric disorders – especially for a predisposition for psychosis – before considering a prescription of TPM. The controversy revolving around the effects of TPM – postulated improvement or on the contrary glutamate-mediated induction or exacerbation of psychotic symptoms – will only begin to be resolved with reliable evidence from future long-term experimental and clinical studies.

Key points

- Topiramate, an antiepileptic drug mainly used in intractable epileptic patients, sometimes may cause exacerbations of positive symptoms and mood disturbances in psychosis
- It may provide some degree of improvement of negative symptoms of schizophrenia
- Because of its weight losing effect, it can preferably be used to decrease of weight gaining side effects of most antipsychotic medication

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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SHORT REPORT

Questionnaire on animal-assisted therapy (AAT): The expectation for AAT as a day-care program for Japanese schizophrenic patients

KAZUHIKO IWAHASHI¹, CHIKAKO WAGA¹ & MITSUAKI OHTA²

¹Department of Neurophysiology, Graduate School of Environmental Health, Azabu University, Kanagawa, Japan, and

²School of Veterinary Medicine, Azabu University, Kanagawa, Japan

Abstract

Animal-assisted therapy (AAT) was developed to promote human social and emotional functioning as a day-care program for psychiatric patients. In this study, we determined which animals 481 schizophrenic patients liked and what they thought about AAT, using an original questionnaire. It was found that more than 80% of the present patients liked animals and that they thought contact with animals was useful as a novel therapy. They had much interest in, and many hopes, for AAT.

Key Words: AAT, schizophrenia

Introduction

Animal-assisted therapy (AAT) has been used as a therapeutic tool for various psychiatric patients, and developed to promote human physical, social, emotional and cognitive functioning, in Europe and America [1,2]. To improve these functions in psychiatric patients, AAT, as an occupational therapy, requires trained animals. There have been few studies on the clinical practice of AAT for schizophrenic patients, or research to determine which AAT mechanism is effective for schizophrenia in Japanese patients.

Schizophrenia is one of the disorders in which an unfavorable outcome is associated with emotional withdrawal and a deficit in social functioning. In this study, we determined which animals Japanese schizophrenic patients liked and what they thought about AAT. We used our original questionnaire for the patients in order to build an AAT program that followed the European and American systems.

Method

Original questionnaire

A total of 481 schizophrenic in- and outpatients, diagnosed according to the ICD-10 criteria, in five psychiatric hospitals in Kanagawa, Kagawa and Tokushima prefectures in Japan were studied. The

subjects were 481 patients (273 male, 208 female; 170 out- and 311 inpatients), aged 14–80 years old (average, 51.2 ± 12.1); diagnosis was F2 (schizophrenia, ICD-10; care periods, under 1 year, 74 (15.8%); 1–3 years, 52 (11.1%); 3–5 years, 40 (8.5%); 5–10 years 76 (16.2%); and over 10 years, 239 (48.3%). We determined their favorite animals and impression of hopes for AAT using a questionnaire, after obtaining informed consent. The questionnaire was carried out in September to October 2001. The data were assessed using the χ^2 -test ($df=1$).

Results

The answers to the questionnaire are presented in Table I 404 (85.2%) of the 481 patients had experience in keeping animals.

A total of 397 patients (82.7%) said they “like animals”, and that their favorite animals were dogs (312 patients), cats (206), birds (150), horses (86), and dolphins (51). On the other hand, disliked animals mentioned were cats (113 people), dogs (86), horses (62), birds (58), and dolphins (51). Other favorite animals were rabbits, hamsters and goldfish, while other disliked animals were snakes, which many patients said they disliked.

Of the patients, 273 (57.6%) said that they wanted contact with animals, and 236 (49.7%, “No idea” not included) thought that contact with animals was

Correspondence: K. Iwahashi, MD, PhD, Professor, Department of Neurophysiology, Graduate School of Environmental Health, Azabu University, 229-8501, Kanagawa, Japan. Tel./Fax: +81 427 69 1930. E-mail: iwahashi@azabu-u.ac.jp

(Received 16 August 2006; accepted 3 January 2007)

ISSN 1365-1501 print/ISSN 1471-1788 online © 2007 Taylor & Francis
DOI: 10.1080/13651500701245973

Table I. Patients' answers to the main questions.

Question	Yes	No idea	No	No response
Have you kept animals?	404 (85.2%)		70 (14.8%)	7
Do you like animals?	397 (82.7%)		83 (17.3%)	1
Do you want to enjoy contact with animals for a change?	273 (57.6%)		201 (42.4%)	7
Do you think the contact with animals is useful as a therapy?	236 (49.7%)	157 (33.1%)	82 (17.2%)	6
Do you not mind my favorite animal coming into the hospital?	216 (46.4%)		250 (53.6%)	15
Do you like well-trained animals better?	316 (69.1%)		141 (30.9%)	24
Do you feel sorry if an animal is used for treatment?	169 (35.6%)	127 (26.7%)	179 (37.7%)	6
Do you know a pet-type robot AIBO?	191 (40.2%)		284 (59.8%)	6
Do you think that AIBO is useful for therapy?	196 (41.8%)	157 (33.5%)	116 (24.7%)	12

useful as a therapy for a change. A total of 250 patients (53.6%) did not mind if their favorite animals came into the hospital, while 216 (46.4%) did mind; 316 patients (69.1%) liked well-trained animals better, and 141 (30.9%) liked animals with a wild and unrestrained character. A total of 169 patients (36.5%) said they would feel sorry if animals were used as tools for therapy, while 179 (37.7%) said "No problem", and 127 (26.7%) said "I don't know".

One hundred and ninety-one patients (40.2%) knew the pet-type robot AIBO, and 196 people (41.8%) thought that an AIBO was useful for a change.

Discussion

As a result of the questionnaire, it was found that more than 80% of the present psychiatric patients liked animals and that they thought contact with animals was useful as a therapy for a change. They had much interest in, and many hopes for AAT. However, 83 (about 20%) patients did not like animals, and thus it may be difficult for them to undergo AAT as a psychiatric therapy; 35.6% of patients felt sorry if an animal was being used for treatment but, on the other hand, 57.6% of patients wanted to enjoy contact with animals. Thus, many patients "like animals", and it is possible that they may treat animals carefully during treatment.

On the other hand, outpatients tended to want contact with animals ($P=0.02$) and thought that AAT was useful for their therapy ($P=0.01$) significantly more than the inpatients. In particular, there were significant differences in the tendencies to dislike animals ($P=0.03$) and to mind animals coming into the hospital ($P<0.01$) between the schizophrenic patients and the non-schizophrenic ones (mood disorders, neurosis, etc.). The schizophrenic patients tended to dislike animals and mind animals coming into the hospital.

Mysophobia (very afraid of dirt) and zoonosis (anxious about infection) were the reasons why the patients minded animals coming into the hospital [3]. It is known that zoonosis involves over 200 kinds of pathogens, for example, bacteria, fungi, viruses,

protozoa, Rickettsia and Chlamydia. However, it is possible to prevent such infection through treatment of the animals by veterinarians. We thus have to think about how to approach animal phobia patients in the future. Unlike real animals, a pet-type robot does not involve the risk of bacterial infection. Therefore, the AIBO may be useful in elderly long-term care facilities for elderly psychiatric patients. Further study is needed.

It is important, as the first step, for patients who like animals, that AAT begins with well-trained and well-treated animals which they have indicated to be their favorites. Also, it is necessary to take good care of the animals in order to avoid stressful conditions.

Based on this questionnaire survey, doctors, nurses and students in Azabu University and JAHA (Japanese Animal Hospital Association), will begin therapy with AAT (light contact with a dog).

It has been reported that AAT might be associated with reductions in fear and anxiety [4]. Actually, it has been reported that Version 3 of the UCLA Loneliness Scale (UCLA-LS) at termination showed improvement compared with baseline scores before AAT in psychiatric patients [5]. Successful examples of AAT in the improvement in domestic activity and negative schizophrenic symptoms have been reported in Hungary and Israel [6,7]. It is reported that AAT seems to be helpful in the rehabilitation of schizophrenic patients and that it may improve anhedonia. More practice is necessary in Japan.

Conclusion

There are few hospitals in which AAT is performed as a psychiatric therapy in Japan. In this study, it was shown that many psychiatric patients who like animals, do not mind animals coming into the hospital, and think AAT may be useful as a therapy for a change. It is also necessary to take good care of the animals in order to avoid stressful conditions, and to prevent any infection between patients and animals. We conclude that it is necessary to establish AAT as a psychiatric therapy suitable for the Japanese culture, as it is in other countries where it is much more advanced.

Key points

- Animal-assisted therapy (AAT) is a program for psychiatric daycare therapy
- AAT has been well studied in Europe and America, but has not yet been much developed in Japan
- We did questionnaire survey of what kind of animal was suitable for treatment of psychiatric patients and have developed a Japanese AAT
- Japanese patients liked dogs and horses and understood that they were to receive AAT as treatment
- We want to develop the AAT program which has proved suitable for Japanese patients

Acknowledgements

This study was supported by the members of Azabu University and JAHA.

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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BOOK REVIEW

***Mental Health Issues and the Media*, Gary Morris. Routledge. 2006. 259 pages. £19.99**

I have a confession to make: I am a slow reader and dread doing book reviews. But this one should have been different. The book is encouragingly slim, it has a topically racy subject, one that I am passionately interested in and, above all, one in which I have been on three sides of the fence – as a newspaper reporter in an earlier life, as a psychiatrist for the last 30 years and as someone with a mental health problem of my own throughout. So why did it take me so long?

Firstly, presentation. This is a worthy book, chock full of information. Morris has a deep knowledge of his subject and is generous to others in the field. But it is just dull. He alludes to the tightropes that anyone approaching the media must walk and especially that between education and entertainment. He quotes a Brookside producer who says that “there is no point in producing challenging storylines unless audiences watch them”. This book has some important messages to give that cried out for presentational pizzazz. Instead, they get lost in over-complicated explanations of simple ideas, repetitious argument and endless use of the same tired examples. I switched off pretty early.

Secondly, content. Like the media programmes it complains about, the book is littered with sins of both commission and omission. My hackles were raised right from the start by an extraordinarily inaccurate representation of the arguments for and against the government’s Draft Mental Health Bill. Even most of the newspapers seemed to grasp these! And as for the things missed out, where is the cultural context? The furore over Frank Bruno (sorry, Frank) was not at all representative of attitudes to young, black, inner-city males who continue to be detained five times as often as their white counterparts, by an institutionally racist system, without a squeak from the public or a *Sun* recantation. And what about the radio? I have to admit to personal bias here but surely this is the medium most sympathetic to mental health problems – intimate and explorative, the media equivalent of the laying on of hands. Hardly a mention.

Thirdly, attitude. Morris rightly castigates the media for its holier-than-thou defence of the “public good” when all it is after is good (i.e. lurid) copy. But

surely we have to shoulder some of the blame too. The problem with negative stereotypes of care, he says, discussing films like *One Flew Over the Cuckoo’s Nest* yet again, is that it “may lead those seeking or receiving mental health care to expect that they will somehow also be violated and abused”. No. The problem is that all too often they are, as the recent survey showing how many female patients are raped in our mixed-sex, violent, dirty, nineteenth-century wards proved. And medicine itself is riddled with stigma towards the mentally ill, amongst staff and patients alike. A hierarchy of acceptability exists between the neuroses, without which no celebrity would be seen dead these days, and the chronic psychotic disorders, unloved by other patients, too unresponsive for career-minded psychiatrists and shunned by the public. Who is in denial here? Mental Health services or the media who point out their shortcomings?

Finally, outlook. I suppose I found this book just too passively pessimistic. Now I hold no brief for those tele-shrinks who hide personal aggrandizement under a cloak of missionary zeal. Nor am I as faint-hearted as the radio psychiatrist who told me we had no hope of changing stigmatising language – we could take lessons from women, the black and minority ethnic communities, gays and lesbians about that one. But somewhere in the middle is an active, practical pathway and not until the last few pages does Morris get around to it.

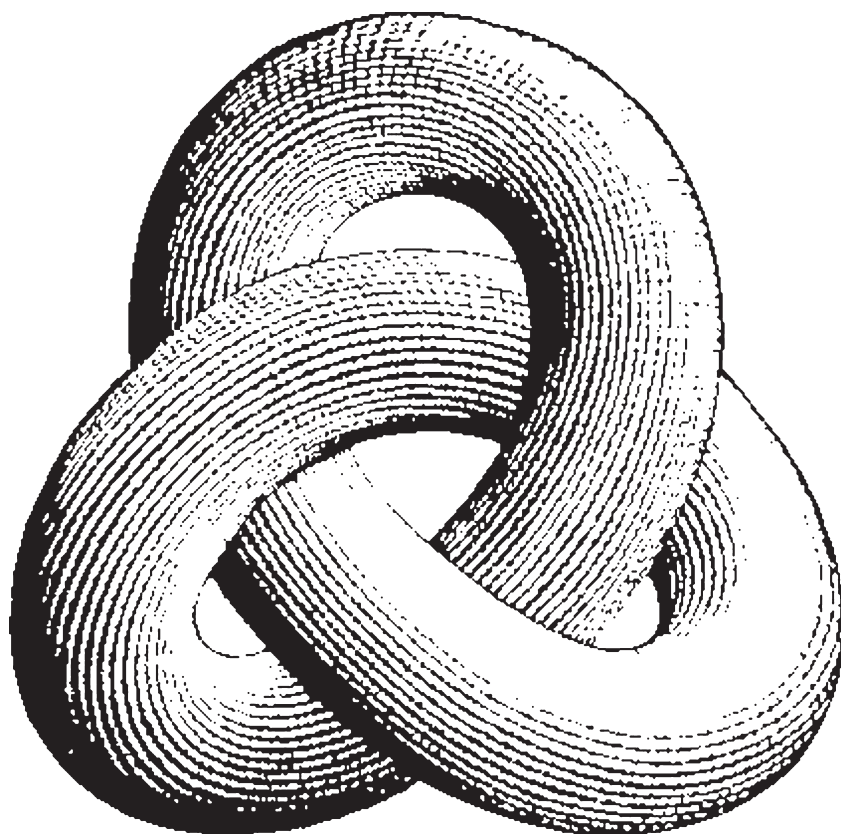
The media is here to stay. Let’s train patients and their carers to use it constructively. Yes, we have to fight stigma and that is a life-long struggle, not a 5-year campaign. But our natural allies in this are the patients who still turn up to hospital and clinic in their overflowing numbers and who, by and large, enjoy careful and conscientious treatment. Let’s repay them by recruiting the media in the fight for better housing, good healthcare, supportive social circles and worthwhile occupations for those with mental health problems everywhere. The rest is just words, however hurtful they may be.

Mike Shooter

*Past President,
The Royal College of Psychiatrists*

ABSTRACTS FROM THE 7TH INTERNATIONAL FORUM ON MOOD AND ANXIETY DISORDERS

3 – 5 December, 2007
Budapest, Hungary



Speaker Abstracts

SO 01. Suicide

SO 0101. Suicide attempt and suicide risk in different depressive syndromes

J. Angst, A. Gamma, R. Gerber-Werder, F. Angst
Zurich University Psychiatric Hospital, Switzerland

Background: There is an ongoing debate about the positive and negative role of antidepressants in suicide attempts and suicides but little life-long data on the suicidality of patients with depressive disorders. The present study analyses the impact of various depressive syndromes and long-term treatments on both suicide attempts and suicides.

Method: The sample consists of 186 unipolar depressive and 220 bipolar depressive or manic patients admitted to the Psychiatric Hospital of the University of Zurich between 1959 and 1963. Their psychopathology on admission was assessed by a comprehensive rating scale for mood disorder (Angst, Battegay, & Poeldinger, 1964) and by a syndrome check list thereafter. A follow-up of the clinical course occurred every five years from 1965 to 1985. The mortality follow-up continued until 2003, by which time 81.3% of the patients had died. More methodological details were published in Angst et al. (2005). Statistics: Survival analyses (Kaplan-Meier and Cox models) data were applied. The analyses of suicide attempts included multiple events/failures.

Results:

1. Risk factors for suicide attempts: broken home, number of previous attempts, time spent in illness, and aggressiveness (statistical trend). Hypochondriasis was found to be protective. No effects were found for gender, agitation, retardation, mixed states or psychotic features.
2. Risk factors for suicide: unipolar depression, time spent in illness, number of previous suicide attempts. An uncertain factor was elevated aggressiveness. No effects were found for gender, psychotic features, mixed states, agitation, retardation, hypochondriasis or broken home.
3. In unipolar depression antidepressants were protective against suicide but not against suicide attempts. In bipolar disorder lithium was protective against both suicide and suicide attempts.

Conclusion: in hospitalised patients with mood disorders, followed over life-time, suicide attempts and suicide differed partly in their risk factors and response to long-term medication.

Key words: suicide, suicide attempts, risk factors, long-term medication

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SO 0102. Prediction and prevention of suicide in mood disorders

Z. Rihmer

National Institute for Psychiatry and Neurology,
Budapest and Semmelweis Medical University,
Budapest, Hungary

Major mood disorders are quite prevalent, but frequently underreferred, underdiagnosed and undertreated illness. The early recognition and appropriate treatment of unipolar and bipolar mood disorders is particularly important, since untreated mood disorders carry extremely high risk of both attempted and committed suicide. Recent studies clearly show that suicidal behaviour in patients with major mood disorders is state and severity dependent that means that suicidality markedly decreases or vanishes after clinical recovery from major depressive episode or from dysphoric mania. However, since the majority of mood disorder patients never commit and more than half of them never attempt suicide, special clinical characteristics of the illness as well as some familial and psychosocial factors should also play a contributory role in the self-destructive behaviour. Considering the clinically explorable suicide risk factors in patients with mood disorders (family and/or personal history of suicidal behaviour, early onset of the disorder, severe depressive episode/hopelessness, agitated/mixed depression, bipolar II diagnosis, comorbid Axis I and Axis II disorders, adverse life situations, lack of social and medical support), in the majority of cases, suicidal behaviour is predictable with a good chance. There are also several evidences that (successful) long-term treatment of unipolar depressives (with antidepressants and/or lithium) and bipolar patients (with mood stabilizers and with antidepressants/antipsychotics) substantially reduces the risk of attempted and completed suicide, even in this high-risk population. Most recent studies also show that supplementary psycho-social

interventions (psychoeducation, and targeted psychotherapies) further improve the results.

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SO 0103. Suicide risk in primary care

JMA Sinclair, Psychiatry Division of Clinical Neurosciences, University of Southampton, UK

Suicide Prevention Strategies have been developed and implemented in many European Countries. Such strategies adopt methods that aim to reduce suicide in high risk groups (particularly those known to secondary psychiatric services) as well as broader population strategies, primarily concerned with reducing access to means of suicide.

Understanding risk factors for suicide in primary care is vital to the success of any Suicide Prevention Programme. These include a diagnosis of depression, alcohol misuse and previous episodes of non-fatal suicidal behaviour. As the majority of people who die by suicide are not known to secondary psychiatric services, but have often seen their primary care physician in the month prior to death, effective delivery of treatments for depression and alcohol misuse (especially in patients with previous episodes of suicidal behaviour) is likely to be an important component of suicide prevention.

Inadequate recognition and treatment of depression in primary care is well recognised as a major risk factor for suicide. Recent studies have also shown that educational programmes can be effective in improving this. However, although alcohol has long been identified as a significant risk factor for suicide, there is less evidence for the benefits of interventions in this group. Over 50% of patients who engage in suicidal behaviour harmfully use alcohol, but they are less likely to access psychiatric services, and are also at increased mortality from other causes.

SO 0104. Do antidepressants raise suicide or agitation in adolescence?

S. Tauscher-Wisniewski
Dept of Child and Adolescent Psychiatry, Medical University of Vienna, Austria
Lilly Research Labs, Indianapolis, USA

There is great concern that antidepressants used in children and adolescents may increase their risk of suicidal thoughts and behavior. In March 2004, the Food and Drug Administration (FDA) issued a public health advisory regarding worsening of depression, suicidal thoughts and behavior in patients treated with the antidepressant drugs fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil),

fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro), bupropion (Wellbutrin), venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron). In February 2005, the agency extended the warning to include all antidepressant drugs. This warning was prompted by analyses of data from placebo-controlled trials of antidepressants suggesting that the drugs were associated with an increased risk of suicidal behavior in children and adolescents.

Suicide in youth is the third leading cause of death between the ages of 10 and 24 years, in the United States. It results in approximately 4600 lives lost each year according to the Center for Disease Control and Prevention (CDC). Suicide affects all youth, but some groups are at higher risk than others. Boys are more likely than girls to die from suicide. Of the reported suicides in the 10 to 24 age group, 82% of the deaths were males and 18% were females. CDC reported in Sept 2007 an increase in suicide rates by 8 percent from 2003 to 2004 which is reason for concern.

If the FDA's conclusion that there may be a causal link between suicide and antidepressants -which was the basis for the black box warning- were correct, we would have expected to see decreases in the suicide rate during the period of declining SSRI prescription rates, but instead we saw an increase in suicide rates, and the increase was greatest in the age range most affected by the decline in SSRI prescription rates. This finding, which is consistent with results of our previous ecological studies of U.S. data suggests that SSRIs confer a protective effect. (Gibbons 2005 & 2006)

Given this concern, how should we modify our clinical approach to pediatric depression? Suicide and suicide attempts are affecting too many youth and young adults. As physicians, we need to make sure suicide prevention efforts and appropriate diagnosis, access to treatment and adequate follow-up care are taking place.

SO 02. Improving signal detection in placebo-controlled studies

SO 0201. Successful studies require the right patients – using the MINI to confirm diagnoses

D.V. Sheehan
University of South Florida College of Medicine, USA

Background: Precise, reliable sampling methods that are easy to implement are central to the success of all scientific research. Study outcomes are heavily influenced by the sample selected. Differences in research results are often due to sampling differences. With the globalization of medical research, the need for diagnostic standardization and consistency has become a high priority. Relying on the individual skills of evaluating clinicians from a variety of backgrounds and training is no longer a

reliable way to collect a homogeneous sample in clinical trials across a large number of sites in many regions or countries.

The MINI (Mini International Neuropsychiatric Interview) is the most widely used structured diagnostic interview internationally in screening patients into psychiatric clinical trials. It has been translated into 44 languages covering about 70% of the world's population. It is made up of 17 disorders. It took a median time of 15 minutes and a mean time of 18 minutes to implement in the international validation studies. Each module has two to three screening questions. If the responses to these screening questions are negative, branching tree logic is used to skip the over the remaining questions in that module and to move on to the next module. Positive responses to the screening questions calls for pursuing further questions to either confirm or disconfirm the presence of the disorder.

Based on the recent concerns about increased risk of suicide on antidepressants in children, adolescents and adults, the Suicidality module of the MINI has been enhanced to collect information and provide documentation to ensure that those at risk are not included in clinical trials and to satisfy the concerns of regulatory agencies in this regard. One of the modules from the MINI Tracking (the Suicidality Tracking Module) is now increasingly used repeatedly during the course of clinical trials to monitor and track the emergence of suicidal behaviors.

The MINI comes in several variants. These include the MINI, the MINI Plus, the MINI Screen, the MINI for bipolar studies, the MINI for psychotic disorder studies, the MINI Kid, the MINI Kid parent version, the MINI Kid screen, the MINI Kid bipolar studies, the MINI Kid for psychotic disorder studies, the MINI tracking. Modules from each of these can be mixed and matched based on the needs of the individual study.

The advantage of the MINI is that it is shorter and easier to navigate and requires less training and experience to use than the other widely used structured diagnostic interviews in psychiatry. However it still requires judgment and skill on the part of the clinician to accurately assess the patient's responses. The clinician's skill and input is used in recording the final response.

One Solution Using a Tablet PC or Laptop PC Direct Entry Source-Data Real Time System

This presentation reports on the use of a direct entry, *source-data* system onto any Tablet PC (computer) touch screen to improve on the current pen on paper system. The same program can be used on any Laptop PCs or Desktop PCs using Windows XP.

Data is entered into the Tablet PC by both the clinician and by the patient at the time of the visit. The electronic data capture file in the PC tablet is the source document. Data is not first recorded on paper and later transcribed. When electronic data capture was first introduced into clinical research all data continued to be collected onto paper case report forms. This data was later transferred to computer by site research coordinators. Such a double entry process added an additional layer of error and data editing. It compounded the traditional inefficiencies and costs and further burdened the research sites.

This eMINI electronic data capture program collects diagnostic data using the MINI structured diagnostic interview. Electronic notes can be added to all items in the structured interview (MINI). Time/date stamps and fingerprint recognition can be recorded on the MINI structured. The program permanently stores all data edits/corrections with a time and data stamp and the name/password/signature and fingerprint of the person either entering data or making later data corrections. This serves as an audit trail on all modifications to data.

It recognizes and stores handwriting, has built in edit checks at the time of data entry, prevents double entries, and eliminates missing data (it does not save data on an incomplete electronic case report). It can be used seamlessly with any voice recognition software to permit dictation of information into the program. It bypasses the need for later keypunching. With a single command, it generates from its database a real-time enrollment log integrated with an associated invoice to the sponsor for work done. It also makes a subject information log report for auditors.

At the end of each visit the captured data can be auto-printed on paper to an office printer via the wireless card in the Tablet PC. These print outs are then filed in a study ring binder. The database file is backed up daily to a server and can be sent regularly to the sponsor for monitoring centrally and for the generation of any data queries. Monitor queries can be appended to all interview information and their resolution tracked. Data can be exported directly in whole or in part to a column delimited file that is readable directly by any statistics program or MS Excel.

Conclusion: Using a structured diagnostic interview like the MINI in screening patients into multi-center clinical trials standardizes the diagnostic screening across all the study sites, reduces diagnostic variability across clinicians and countries and ensures consistency in eliciting DSM IV and ICD 10 diagnostic criteria.

Disclosure: Dr. Sheehan is a shareholder in and Consultant to Medical Outcome Systems which markets the computerized versions of the MINI.

II. Educational Objectives:

1. Understand approaches to improving diagnostic precision using a structured diagnostic interview in accurately selecting the right patients in clinical trials
2. Understand the advantages and capabilities of the various structured diagnostic interviews
3. Appreciate the limitations of various structured diagnostic interviews

SO 0202. Do effectiveness studies tell us the real truth?

H-J. Moeller

Department of Psychiatry, University of Munich, Germany

The results of so-called 'effectiveness studies' have recently cast doubt on the superiority of the second generation antipsychotics (SGAs). For example, the CATIE study found no major differences between the SGAs and perphenazine, the chosen representative of the first generation antipsychotics (FGAs). The results of the CUtLASS study indicated that FGAs have no disadvantages in terms of quality of life, symptoms or cost of care. A third effectiveness study, by McCue et al., even found that haloperidol (together with olanzapine and risperidone) was more effective than aripiprazole, quetiapine and ziprasidone in improving patients' mental status.

The methodological problems of effectiveness studies will be presented, and accompanied by a discussion of the discrepancy between the results of phase III efficacy studies and effectiveness studies. Starting with the effectiveness studies on antipsychotics, the presentation will then proceed to discuss such studies in the field of drug treatment of unipolar and bipolar depression, such as STAR*D and STEP-BD.

SO 0203. Interpreting Evidence in Clinical Papers and Lectures

K.H. Sheehan

University of South Florida College of Medicine, USA

Background: Clinicians are often bewildered by the vocabulary and methodology of clinical trials. When can you have confidence in a set of results? When should you suspect you are being hoodwinked or tricked? This presentation is designed to help clinicians assess the quality of clinical trials. We will also go over some of the tactics drug companies and academics sometimes use to overplay their results.

Educational Objectives: At the conclusion of this presentation, the participants should be able to:

1. *Appreciate* the many ways in which clinicians can be misled when information from clinical studies is used to market a position and to influence their prescribing practices.

2. *Recognize* the most common tactics used to overplay the strength of evidence in clinical treatment studies and in meta-analyses and be able to see through and beyond these tactics.
3. *Discuss* the strength of the evidence for effective treatments for the spectrum of anxiety and mood disorders.
4. *Evaluate* evidence presented in clinical trials and assess the level of confidence they can attach to the evidence presented in lecture slides, handouts, research papers, posters and pharmaceutical company sales aids.

SO 0204. Increased severity of depression increases the chances of a difference from placebo

S. Montgomery

Imperial College School of Medicine, London, UK

The chances of an antidepressant demonstrating a difference from placebo is low. The proportion of studies which are successful, even for an established antidepressant such as imipramine, were estimated at 32% in the pivotal studies over a ten year period. Recent experience suggests that this proportion is dropping as the number of inconclusive studies rise.

There are many factors involved but all point to the failure of current study diagnostic practices to select an assay sensitive population. An analysis of data from placebo-controlled studies shows a high placebo response rate in mild depression and a lower placebo response rate in severe depression. Increasing the severity of depression at baseline has produced better assay sensitivity provided that these designs can control for potential rater exaggeration.

SO 03. Treatment Resistant Depression**SO 0304. Patients with treatment resistant depression in my practice**

I. Bitter

Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

Checking almost 30 years of history of my practice I identified patients with treatment resistant depression. The majority of them have/had a diagnosis of bipolar disorder, some of them had comorbidities with anxiety disorders. In some cases the diagnosis of bipolar disorder was rather difficult.

The use of a mood stabilizer including the use of an atypical antipsychotic resulted in improvement in a number of patients with bipolar disorder, however compliance with the long term treatment has been a major issue. In some cases electroconvulsive treatment (ECT) was used, not all patients responded to this treatment either. Considering the history of convulsive treatment and the place

of the 7th International Forum on Mood and Anxiety Disorders a very short history of the origins of convulsive treatment will be presented. Laszlo Meduna-who discovered the treatment effect of convulsions-worked in Budapest.

Case vignettes of patients with treatment resistant depression will be presented.

SO 04. Treatment of depression and anxiety in the “post SSRI era”

SO 0401. What are the future challenges in the treatment of Mood Disorders

A. Wade

CPS Research, Glasgow, United Kingdom

The introduction of the Selective Serotonin Reuptake Inhibitors in the 1980s revolutionized the treatment of mood disorders, by offering much better tolerability than the previously used tri- and tetracyclic antidepressants.

However problems such as low compliance, delayed onset of action, poor response rates and too short treatment length persisted. The emergence of newer, dual-acting antidepressants, such as SNRI or NDRI in the 1990s still failed to address these issues adequately.

Much of the data available to clinicians about antidepressants is derived from the artificial environment of clinical trials designed to meet regulatory requirements and with clearly defined inclusion and exclusion criteria. The practical relevance of these results to daily clinical practice is being increasingly challenged. Mounting cost pressures within virtually all health-care systems however has emphasised the potential importance of these differences and the pharmacoeconomic evaluations which can be derived from them.

Patient focused evaluation parameters, such as treatment satisfaction, quality of life, social integration and ability to work or function are likely to become increasingly important in helping to evaluate the practical relevance of some traditionally measured outcomes. They are also likely to lead towards a more patient focused approach to the treatment of mood disorders.

The presentation will discuss these issues and will present examples in which parameters such as quality of life have been integrated into clinical study programmes.

SO 0402. Seasonal Affective Disorder-nature's influence on mood

S. Kasper

Department of Psychiatry and Psychotherapy, Medical University Vienna, Wien, Austria

The influence of seasons and weather on mood has been known and described anecdotally for

decades. Winter type seasonal affective disorder (SAD) is a subtype of a recurring mood disorder with regular onset of major depressive episodes during fall or winter followed by remission or hypomanic episodes during the successive spring/summer period. Bright light therapy (BLT) is considered to be the first choice of treatment for patients with SAD. However a substantial percentage of SAD patients does not show sufficient response to BLT or the use is limited due to logistic problems or side effects. These patients require psychopharmacological treatment either in addition to or instead of BLT.

Escitalopram is a SSRI with high affinity to the serotonin transporter (5-HTT) and a unique interaction with an affinity-modulating binding site of the 5-HTT, which has been shown to augment the efficiency of serotonin reuptake. Escitalopram has shown to be efficacious and well-tolerated in randomized controlled trials in major depressive disorder and anxiety disorders.

Twenty SAD patients were included in an 8-week drug surveillance (Pjrek et al 2007). Patients were treated with open-label escitalopram at a dosage of 10 to 20 mg per day. Efficacy assessments included the Structured Interview Guide for the Hamilton Depression Rating Scale (SAD version; SIGH-SAD), the Clinical Global Impression (CGI) and the Social Adaptation Self Evaluation Scale (SASS). Side effects were monitored with the UKU Side Effect Rating Scale. From week 2 onwards, escitalopram significantly reduced SIGH-SAD score and CGI severity score ($p < 0.001$). From week 4 onwards, the SASS score was also significantly improved ($p < 0.05$). The response rate (SIGH-SAD $< 50\%$ of baseline value) after treatment for 8 weeks was 95%, the rate of remission (SIGH-SAD ≤ 7) was 85%. Side effects were mild to moderate and did not lead to cessation of therapy.

Our study supports the evidence that antidepressants are a valuable treatment option for patients suffering from SAD.

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SO 0403. Premenstrual Dysphoric Disorder – a condition worth to treat?

E. Eriksson

Department of pharmacology, University of Göteborg, Göteborg, Sweden

Approximately 5% of all women of fertile age are afflicted by a sex hormone-dependent condition characterised by severe symptoms appearing regularly during the luteal phase of the menstrual cycle,

i.e. *premenstrual dysphoric disorder* or *severe premenstrual syndrome*. Irritability is the most prominent symptom, but depressed mood, affect lability, tension and various somatic complaints are also parts of the syndrome.

The fact that mild premenstrual symptoms are present in a majority of women must not conceal the fact that the severe variant leads to a marked reduction in life quality and warrant effective treatment. Many studies demonstrate that serotonin reuptake inhibitors (SSRIs) reduce premenstrual symptoms, that they in this sense are superior to non-serotonergic antidepressants, and that this effect of SSRIs displays a short onset of action enabling intermittent treatment during luteal phases only.

In this presentation, a number of yet unresolved issues related to this treatment will be discussed on the basis of data from previous studies. It will hence be suggested a) that certain symptoms within the premenstrual syndrome, such as irritability, are much more inclined to respond to treatment than other symptoms within this syndrome, in particular when the treatment is administered intermittently, and b) that there is in fact no single SSRI-responsive psychiatric condition displaying a higher response rate than premenstrual irritability.

These conclusions gain support also from a recent study in which the effect of the allosteric SSRI escitalopram (10 or 20mg; fixed doses; intermittent treatment) was assessed for three months in 158 women with PMDD. Escitalopram hence was found to exert a marked and dose-dependent effect, the difference between the higher dose of escitalopram and placebo with respect to the primary effect variability (=the sum of VAS-rated irritability, tension, depressed mood and affect lability) being significant on the $p = 0.0000003$ level. As predicted, while irritability was the symptom displaying the most clear-cut difference between active treatment and placebo, the somatic symptoms were those being least influenced.

SO 0404. Are SSRI still “state of the art” or have we reached the “post SSRI era” in the treatment of Major Depressive Disorder?

G. I. Papakostas

Massachusetts General Hospital, Harvard Medical School, Boston, USA

Systematic pharmacological treatment of mood disorders commenced in the 1950s with the introduction of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs).

While these compounds have been proven effective, side effects (including those that pertain to both tolerability as well as safety) were a major limiting factor for the use of these compounds.

The introduction of Selective Serotonin Reuptake Inhibitors (SSRI) in the 1980s revolutionized the

treatment of mood disorder largely owing to their improved tolerability and safety profiles when compared to the MAOIs and TCAs.

However, there is emerging evidence suggesting that newer agents may possess advantages in terms of efficacy and/or tolerability over the traditional agents in the SSRI class. These newer agents include those that simultaneously influence serotonergic and noradrenergic functioning including venlafaxine, milnacipran and mirtazapine, the norepinephrine dopamine reuptake inhibitor bupropion, or escitalopram, a highly selective SSRI which differs from the other SSRIs by an additional allosteric mechanism of action at the serotonin transporter,

This presentation will describe the evolution of antidepressant treatment and will present the current knowledge on comparative efficacy and tolerability of currently available treatments, helping the attending physician to choose medications, based on scientific evidence.

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SO 05. The importance of sleep in depression

SO 0501. Importance of sleep disturbance in mood and anxiety disorders

D. S. Baldwin

Clinical Neuroscience Division, University of Southampton, United Kingdom

Disturbed sleep is so common a symptom in mood disorders, that is used to help support the diagnosis for major depressive episodes (in unipolar and bipolar disorder) and dysthymia: disturbed sleep is also listed within the diagnostic criteria for generalized anxiety disorder (GAD) and post-traumatic stress disorder. Furthermore, longitudinal studies indicate that complaints of disturbed sleep (in the absence of depression) at baseline are associated with an increased risk of depression at follow-up. Insomnia is often considered one of the most distressing symptoms by people experiencing depres-

sion, and is known to be associated with reduced quality of life, and increased risk of recurrence and suicide. Insomnia can be a troublesome and persistent residual symptom following treatment with antidepressants or cognitive behaviour therapy, and is often difficult to treat.

Depressed patients show characteristic abnormalities on sleep EEG, including shorter total sleep time, longer sleep latency, less slow wave sleep, reduced REM sleep latency and greater REM sleep density, and most effective antidepressants have been found to suppress REM sleep. There is a rather limited correlation between these 'objective' EEG findings and 'subjective' complaints of insomnia, and depressed patients tend to overestimate periods of wakefulness, this being more marked in patients with severe symptoms. Previous research from our group has indicated that the first-degree relatives of depressed patients show similar distortions of the perception of sleep, this not being the case in the relatives of controls. Insomnia is common in patients with anxiety disorders, but has been the subject of relatively little research. However, reduced REM sleep latency is not consistently seen in GAD or obsessive-compulsive disorder, supporting the contention that the neurobiology of these disorders differs from that in major depression.

A range of strategies have been employed to improve the sleep of depressed patients, either as a treatment for a troublesome residual symptom or as an attempt to enhance overall antidepressant efficacy. These studies will be reviewed and potential new treatment approaches will be discussed.

SO 0502. Treating sleep with eszopiclone plus SSRIs in MDD or GAD

S. Montgomery

Imperial College School of Medicine, London, United Kingdom

Insomnia is one of the hallmark diagnostic criteria of major depressive disorder (MDD) and generalized anxiety disorder (GAD). In fact, insomnia may be a symptom of depression, a side effect of antidepressant treatment, a predictor for subsequent development of depression, or an indicator of depression relapse. Insomnia and generalized anxiety disorder (GAD) are also highly prevalent conditions which commonly co-exist and have considerable symptomatic overlap. Despite these findings, very few studies have been conducted to determine the effectiveness of targeted insomnia treatment with a hypnotic in addition to targeted treatment of psychiatric disease with an SSRI in patients with insomnia comorbid with MDD or GAD.

Two large studies have been conducted to address this: one in patients with insomnia comorbid with MDD and the other in patients with insomnia comorbid with GAD. Both were randomized, dou-

ble-blind, placebo controlled studies with approximately 600 patients each. Patients received 10 weeks of SSRI (fluoxetine in the MDD study, escitalopram in the GAD study) and were randomized to nightly eszopiclone 3mg or placebo for 8 weeks. For the last 2 weeks, eszopiclone was replaced with single-blind placebo to evaluate rebound and withdrawal effects. Sleep, daytime function, measures of psychiatric disease, and safety were measured throughout the treatment period.

In both studies eszopiclone/SSRI co-therapy was well-tolerated and resulted in significantly improved sleep and daytime function across the 8 weeks of hypnotic/SSRI co-therapy. In addition to improving sleep, co-administration of eszopiclone with SSRI resulted in a greater change in measures of mood (HAMD-17, HAM-A), an increase in the number of responders, and an increase in the numbers of subjects achieving remission. There was no evidence of tolerance over the treatment period, and, following abrupt discontinuation, there was no evidence of rebound or withdrawal effects.

Interestingly, the pattern of sleep improvements in GAD patients co-treated with eszopiclone differed from the pattern observed in MDD patients. In GAD, the impact on sleep occurred immediately and was then maintained, whereas in MDD, sleep improved early and continued to gradually increase over the 8-week, double-blind treatment period. Additionally, the therapeutic advantage of eszopiclone co-therapy over SSRI monotherapy in treating sleep during the double-blind period was maintained during the single-blind run-out period in the depression study, but not in the GAD study. The reasons for these differences are unclear. Evidence suggests that insomnia has a different relationship to GAD than to MDD when it occurs comorbidly with these conditions.

SO 0503. Effect of Agomelatine on sleep in depression

M. Lader

Institute of Psychiatry, King's College London, London, United Kingdom

Agomelatine is a novel antidepressant with agonist actions on melatonin₁ and melatonin₂ receptors, together with antagonist properties on 5-HT_{2C} receptors. Several studies have shown that it has efficacy in depressed patients, both in the short- and in the long-term. This efficacy extends to severely depressed patients, in whom it is equivalent to venlafaxine. It lessens anxiety within the depressive syndrome, and is equivalent to paroxetine.

Depression and sleep disorders are intimately inter-related. Because of its melatonergic properties, particular interest has centred on agomelatine's effect on sleep, especially as an important symptom within depression. Comparisons with venlafaxine,

using the Leeds Sleep Evaluation Scale showed that ease of getting to sleep was superior in the agomelatine than the venlafaxine group. Quality of sleep showed a similar pattern. Visual analogue scales showed superiority for agomelatine for daytime sleepiness and feeling well at the 1-week point only.

Polysomnographic (PSG) studies demonstrated that the % Total Sleep Time increased significantly over 6 weeks of administration of agomelatine, as did awakenings after sleep onset. Sleep architecture in the depressed patients tended back towards the normal pattern.

Agomelatine has a low incidence of unwanted effects. Furthermore, unlike benzodiazepine receptor agonists and SSRIs such as paroxetine, the cessation of agomelatine is not attended by a significant increase in discontinuation-emergent effects.

It is concluded that agomelatine has an unusually favourable risk/benefit ratio for an antidepressant. In addition its beneficial effects on sleep measures and daytime functioning suggest a particular role for this compound in the treatment of depressive disorders characterised by pronounced and distressing sleep disturbance.

SO 0504. Sleep deprivation: a forgotten tool?

F. Benedetti

Istituto Scientifico Universitario Ospedale San Raffaele, Department of Neuropsychiatric Sciences, Milano, Italy

Psychiatric chronotherapeutics is the controlled exposure to environmental stimuli that act on biological rhythms in order to achieve therapeutic effects in the treatment of psychiatric conditions. In recent years some techniques (mainly light therapy and sleep deprivation) have passed the experimental developmental phase and reached the status of powerful and affordable clinical interventions for everyday clinical treatment of depressed patients. These techniques target the same brain neurotransmitter systems and the same brain areas as do antidepressant drugs, and should be administered under careful medical supervision. Their effects are rapid and transient, but can be stabilised by combining techniques among themselves or together with common drug treatments.

Antidepressant chronotherapeutics targets the broadly defined depressive syndrome, with response and relapse rates similar to those obtained with antidepressant drugs, and good results are obtained even in difficult-to-treat conditions such as bipolar depression. While disruption of sleep-wake and activity-rest rhythms is a known trigger of mood episodes in bipolar disorder, specific combinations of extended wake and light during depression, and extended bedrest and dark during mania, can help to rapidly restore euthymic conditions.

Chronotherapeutics offers then a benign alternative to more radical treatments for severe depression on psychiatric wards, giving to the patients similar rates of response but with the advantage of rapidity of onset and lack of side effects.

SO 06. Everyday problems in Treating depression-Focus on SNRIs

SO 0601. Recognising and effectively treating depression

Y. Lecrubier

Hôpital la Salpêtrière, INSERM, Paris, France

More people die in Europe from suicide than from road accidents. The lifetime prevalence of major depression is 20% for women and 7% for men. Postpartum depression occurs following one pregnancy in 10. Depression is a leading cause of disability, workplace absenteeism, productivity loss, as well as increased use of health care resources and decreased quality of life. Numerous studies have shown that only about 50% of depressed patients are recognized as such in primary care. A recent study suggested an improvement, since primary care physicians recognized nearly 80% of cases of depression and prescribed antidepressants to half of them. However, 45.0% of the patients classified as depressed were, in fact, not cases of depression according to ICD-10 criteria. The use of a careful multi-level algorithmic approach to the treatment of depression was investigated by Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. About half of the participants became diagnosis-free after two levels (treatment with first-line or second-line antidepressants). Over the course of all four levels, about 70% of those who did not withdraw from the study became diagnosis-free. In a recent international study of everyday management of depression, however, we observed that only about 15% of patients became symptom free. In spite of this low level of remission primary care or psychiatrist only rarely increased the dose of antidepressant or switched to another medication as suggested by different guidelines and as tested by the STAR*D study. Current guidelines recommend a minimum of 3 to 6 months antidepressant treatment and population studies have confirmed the efficacy of these guidelines in preventing recurrence. Several studies of real world usage have reported that 25 to 35% of all initial antidepressant prescriptions are not renewed thus limiting treatment to about one month.

Depression is a common and frequently lethal disease which must be sought actively by primary care and specialist health professionals. Antidepressant treatment can be very effective but only when used correctly at adequate doses and for a sufficient

duration. Although new improved antidepressants are obviously desirable, the recognition of depression and the correct use of currently available antidepressant drugs could greatly improve the management of depression.

SO 0602. Treating depression with SNRIs, who will benefit most?

M. Isaac

South London & Maudsley NHS Trust/Institute of Psychiatry, London, United Kingdom

SNRIs, venlafaxine, milnacipran and duloxetine, have been shown to have superior antidepressant activity to SSRIs especially in more severe depression. Some patients, however, respond better to SNRIs than others. Milnacipran has been well studied from this point of view. The presence of the T allele of the NET-182C polymorphism of the noradrenaline transporter is correlated with a greater response to milnacipran, whereas the A/A genotype of the NET G1287A polymorphism is associated with a slower onset of response. The G/A genotype polymorphism of BDNF G196A is associated with a better antidepressant response to milnacipran but also to the SSRI, fluvoxamine. This polymorphism is therefore likely to be involved in common downstream pathway of antidepressant action rather than a pathway specific to certain antidepressants. Tolerability can also be influenced by polymorphic differences. Serotonin transporter VNTR polymorphism and the serotonin transporter-gene-linked polymorphic region (HTTLPR) polymorphism influence tolerability of drugs acting primarily through the inhibition of 5-HT reuptake, such as SSRIs and venlafaxine, which has a greater than 30 fold selectivity for the serotonin transporter. In contrast, these gene polymorphisms have no effect on the antidepressant response or tolerability of milnacipran which has similar affinity for both 5-HT and NA reuptake. Patients with low pretreatment levels of plasma 3-methoxy-4-hydroxyphenylglycol (pMHPG) have a better response to milnacipran. These recent genomic and neurochemical data confirm that milnacipran, in contrast to SSRIs and venlafaxine, has a major impact on the noradrenergic system. Differences in metabolism determined by genetic variables in CYP2D6 activity are a major determinant of venlafaxine levels to such an extent that genetically determined decreases in CYP2D6 activity have been associated with cardiovascular toxicity. Milnacipran, which is not metabolised by the enzymes of the CYP450 system is not influenced by polymorphism of these enzymes. These data suggest that pharmacogenetic data may become a precious aid to help clinicians choose the most antidepressant medication for a particular patient.

SO 0603. Initial effectiveness, partial and full remission in depression – focus on long-term treatment

S. Dursun

Neuroscience and Psychiatry Unit, University of Manchester, United Kingdom

Full remission, the absence of all significant symptoms of depression over six months, is the ultimate goal of the depressed patient and his physician. Remission takes time and studies have shown that remission rates continue to rise for at least three months after initial improvement. Increasing the dose of an antidepressant can increase and accelerate the rate of recovery. Depression is a recurrent condition with a cumulative probability of recurrence of 40% by 2 years and 70% by 5 years after the first depressive episode. In addition the risk of recurrence increases dramatically with each new depressive episode. It has been shown with many antidepressants that continuing treatment beyond the acute response significantly decreases the risk of recurrence compared to placebo. For example, in a double-blind study, 214 patients in remission from a depressive episode following treatment with milnacipran were randomized to continue milnacipran or to switch to placebo for one year. Of the patients switched to placebo, 27% had a new depressive episode during the following year compared to only 15% of those continuing on milnacipran ($p < 0.05$). In this study 45% of the original population of patients treated with milnacipran achieved remission after 6 weeks of treatment. Of these 82% were still in remission after a total of 70 weeks of maintenance treatment with milnacipran. In spite of the importance of maintaining treatment in euthymic patients who have recovered from a depressive episode many patients do not continue. Among the principal reasons for this are side-effects and worries of psychological or physical dependence. There is no evidence that milnacipran causes dependence and it is not associated with any discontinuation syndrome. Milnacipran is safe in overdose and no fatalities have been recorded.

Clearly treatment with an effective, well tolerated antidepressant with few or no drug interactions, steady blood levels, no withdrawal effects and a simple and regular dosing schedule is likely to have the best compliance and ultimately produce the greatest long-term benefit for the patient.

SO 0604. Tolerability of SNRI antidepressants

S. Montgomery

Imperial College School of Medicine, London, UK

Although selective serotonin reuptake inhibitors (SSRI) are the principal first-line treatment of depression, serotonin and noradrenaline reuptake

inhibitors (SNRI) are increasingly used where SSRIs fail to provide sufficient antidepressant efficacy. Although, by definition, all three SNRIs inhibit the reuptake of both serotonin and noradrenaline, they do so with differing affinity ratios. Venlafaxine has a 30 fold higher affinity for serotonin than noradrenaline while duloxetine has a 10-fold selectivity for serotonin. Only milnacipran is balanced between the two neurotransmitters with an approximately equal potency for the inhibition of reuptake of serotonin and noradrenaline. This difference in selectivity is possibly one of the reasons for the different tolerability profiles of the three SNRIs.

The most frequent adverse event with the SNRI is nausea with a globally similar frequency to the SSRIs. As would be expected, adverse effects related to a noradrenergic stimulation, such as dry mouth, sweating and constipation, are found systematically more frequently with the SNRIs than the SSRIs. At true SNRI doses, venlafaxine is associated with dose-dependent cardiovascular phenomena (principally increased blood pressure), an effect which is less important with duloxetine and absent with milnacipran. Hepatotoxicity, which does not exist with the other SNRIs, is a serious potential adverse effect of duloxetine which is aggravated by pre-existing hepatic insufficiency and alcohol use. The predominantly serotonergic profile of venlafaxine and, to a lesser extent, duloxetine is probably related to their frequent association with drug-related sexual dysfunction at a rate equivalent to the SSRIs. In contrast, the prevalence with milnacipran appears to be considerably lower. Safety in overdose is a legitimate concern with all antidepressants and fatalities have been reported due to overdose of venlafaxine alone or in combination with other compounds often following a serotonin syndrome. At the present time no cases of overdose with duloxetine have been published. Milnacipran is safe in overdose and no fatalities have been recorded. Ingestion of doses equivalent to one month's supply at the recommended dose have been reported with no serious effects other than sedation.

SO 07. OCD: defining new boundaries

SO 0701. Should OCD still be classified as an anxiety disorder?

N.A. Fineberg^{1,2}, S.R. Chamberlain^{1,2}, K. Craig^{1,2}
¹National OCD Service, University of Hertfordshire, Queen Elizabeth II Hospital, Welwyn Garden City, Herts, UK, ²Dept. of Psychiatry, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK

Under the DSM-IV, OCD is categorized as an anxiety disorder and the central role of anxiety in mediating symptoms is emphasised. Arguably, anxiety

fulfils a pivotal role in OCD: obsessions contribute to anxiety and compulsions are performed to avoid or reduce this anxiety. However, for many, performance of compulsions has no effect or even exacerbates anxiety. Comorbidity in OCD clusters more with other compulsive disorders, such as Tourette's Syndrome, body dysmorphic disorder, trichotillomania, etc, than with anxiety disorders. The same is true for rates of co-segregation in family studies. OCD can be further differentiated by its early age of onset, chronic course, gender ratio and selective response to high-dose serotonin reuptake inhibitor drugs. ICD-10 recognised anxiety with and without autonomic arousal and separated OCD from anxiety disorders, categorising it with neurotic, stress-related and somatoform disorders.

Endophenotypes are heritable traits lying on the pathway between genes and expressed symptoms, considered to more closely represent genetic risk for complex polygenic mental disorders than overt behaviours do. They may thus be a more sensitive measure for differentiating OCD from overlapping psychiatric disorders. Using endophenotypes such as neurocognitive measures, imaging and molecular data as well as results from demographic, comorbidity, family and treatment studies, we may map the nosological relationships of OCD to other putatively related mental disorders. In this way we have identified failures in the inhibition of motor and cognitive behaviour, and cognitive inflexibility as candidate endophenotypes for OCD. These cognitive domains are thought to reflect functional integrity within neural circuits involving the frontal cortex and subcortical connections, including subthalamic nucleus, rather than the classical fear-circuitry underpinning anxiety.

These findings support the argument for separating OCD from the anxiety disorders, however comparative data is lacking and an alternative position for OCD remains to be established. Despite high levels of comorbidity, endophenotypic differences also appear to separate OCD from depression and schizophrenia. Although OCD and addictions share endophenotypic similarities, they show lower than expected comorbidity and familial relationships. Emerging evidence suggests stronger relationships between OCD, Tourette's syndrome, body dysmorphic disorder, hypochondriasis, grooming disorders, obsessive compulsive personality disorder and paediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS). Studies designed to delineate cause, consequence and common factors are a challenging but essential goal for future research in this area.

SO 0702. Is OCD a unitary disorder?

D.J. Stein
 University of Stellenbosch, Tygerberg-Cape Town, South-Africa

A number of different approaches to obsessive-compulsive disorder and to the obsessive-compulsive spectrum of disorders have been taken over the years, with different authors emphasizing the psychodynamic, cognitive-behavioral, and neurobiological mechanisms thought to underlie various OCD subtypes and spectrums. There is growing evidence that the recognition of certain subtypes of OCD may be useful in clinical settings; these include early-onset OCD, OCD with tics, and OCD with predominant hoarding. Advances in the cognitive-affective neuroscience of obsessive-compulsive disorder (OCD) may be useful in validating such subtypes. Furthermore, such advances may also suggest novel ways of delineating the obsessive-compulsive spectrum of disorders in terms of cortico-strially mediated control and reward mechanisms. The space defined by the obsessive-compulsive spectrum of disorders is likely best conceptualized as multidimensional in nature.

SO 0703. OCD and schizophrenia: integral or overlapping

J. Zohar

Psychiatry A, Chaim Sheba Medical Centre, Israel

Phenomenologically, “schizo-obsessive” patients represent both typical presentation of schizophrenia and typical presentation of OC symptoms. Overall, reports from research groups around the globe, including more than 2000 patients altogether (with OCD or OC symptoms in schizophrenic patients) provide compelling evidence that the odds of OCD in schizophrenic patients are considerably higher than expected. Since the comorbidity of schizophrenia and OCD is much higher than expected, it might suggest a common underlying pathophysiological linkage between the two disorders.

The course of the illness in “schizo-obsessive” patients is distinctly different – poorer – to that of schizophrenia. When morbid risk for OCD, Obsessive compulsive personality disorder (OCPD) and “schizo-obsessive” were grouped together, the significance of between-group differences became stronger ($p=0.0002$). These findings are in line with the hypothesis that “schizo-obsessive” disorders might be familial.

Brain circuitry suggests that there is a combination of the relevant circuitry in individuals with “schizo-obsessive” disorder. Neurocognitive tests carried out in “schizo-obsessive” and schizophrenic patients without OCD suggest that the best fit of the “schizo-obsessive” patients’ results is of a simple combination of schizophrenia and OCD. Pharmacologic or psychological interventions are also in line with the above findings; probably a combination of antipsychotic and antiobsessional medications is better than either alone. Looking at the emerging data, the possibility of recognizing “schizo-obses-

sive” as a schizophrenia subtype will be presented and discussed.

SO 0704. OCD and cognitive function

S.R. Chamberlain, L. Menzies, N.A. Fineberg

Department of Psychiatry, University of Cambridge, Cambs, United Kingdom

National OCD Treatment Service, Queen Elizabeth II Hospital, Herts, United Kingdom

Trichotillomania (TTM) and obsessive compulsive disorder (OCD) are putative obsessive-compulsive spectrum disorders characterised by difficulties suppressing pathological habits. OCD is currently regarded as an archetypal disorder of compulsivity, whereas TTM is classified as an impulse control disorder (DSM-IV). Cognitive deficits reported in patients with these disorders are thought to stem from underlying dysregulation of fronto-striatal circuitry. We compared OCD and TTM patients on objective tests of response inhibition (stop-signal task) and cognitive flexibility (set-shifting task). Both OCD and TTM showed impaired motor impulse control ($p<0.05$) whereas only OCD patients showed additional impairment with cognitive flexibility ($p<0.05$) (Chamberlain et al., 2006). These data suggest different impairments in inhibitory functions underlie the manifestation of impulsive and compulsive features of OCD and TTM.

In comparison to matched controls without a family history of OCD, unaffected first-degree relatives of OCD patients also showed impaired motor inhibitory control ($p<0.01$) and cognitive flexibility ($p<0.01$). These deficits were comparable to those reported in patients (Chamberlain et al., 2007). The same individuals were also subjected to structural brain imaging using MRI. Large scale brain systems were identified in which anatomical variation was associated with variation in inhibitory control (incorporating such regions as the right inferior frontal gyrus and orbitofrontal cortex). Familial effects on variation of MRI markers of inhibitory control were found (Menzies et al., 2007). These results support the utility of objective neuropsychological and neuroimaging markers in the search for endophenotypes. It is hoped that such markers will be valuable for further exploring the aetiology and pathophysiology of OCD and related spectrum disorders.

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SO 08. Pain: a neglected symptom of affective disorder

SO 0801. Prevalence of pain in depression

B. Bandelow

Department of Psychiatry and Psychotherapy, University of Göttingen, Germany

Painful physical symptoms are present in two thirds of major depressive disorder patients. Pain can impair treatment outcome and obscure diagnosis, and the severity of pain is a predictor of poor depression and health-related quality of life outcomes. Physical symptoms are more prevalent among women, elderly, and socially underprivileged persons. Relative to depression alone, depression plus pain is associated with significant functional limitations and economic burdens.

There is also a high overlap between depression, anxiety symptoms, and pain syndromes associated with somatization disorder or fibromyalgia.

Neurons descending from the raphe nucleus and the locus coeruleus to the spinal cord serve to inhibit input from the intestines, the skeletal muscles and other sensory inputs. A dysfunction at the level of the serotonergic and noradrenergic neurons can thus result in physical painful symptoms. Antidepressants inhibiting serotonin and norepinephrine reuptake (SNRI) have been shown to be effective in managing pain symptoms associated with depression. Dual action antidepressants also were used successfully to treat fibromyalgia. Fibromyalgia, neuropathic pain and central pain also respond to pregabalin, a calcium channel modulator which was also effective in treating generalized anxiety disorder.

Better recognition, assessment, and treatment of painful physical symptoms may enhance outcomes of depression therapy.

SO 0802. GAD, Pain and Pregabalin

C. Altamura, E. Mundo

Dept. of Psychiatry, University of Milan, IRCCS Fondazione Ospedale Maggiore Policlinico Mangiagalli, Milano, Italy

Generalized Anxiety Disorder (GAD) is a prevalent psychiatric condition with approximately 2% of the adult population in the community affected (12-month prevalence) [1] and is associated with significant impairment in quality of life and functional abilities. Core symptoms of GAD are often accompanied by somatizations and painful physical symptoms. On the other hand, patients with different painful syndromes show an increased risk of anxiety

syndromes or disorders such as GAD. Therefore, the strong relationship between GAD and pain is of particular interest in the psychiatric clinical practice and needs to be specifically considered in the pharmacological choice. A variety of pharmacological agents have been shown to be effective in treating GAD, with Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors such as Venlafaxine being considered first-line compounds. Benzodiazepines, Buspirone and psychological interventions have demonstrated positive effects in GAD patients as well. Nevertheless, there is a clinical need for alternative drug treatments, as many GAD patients do not achieve a complete response and experience significant adverse effects. In addition, these pharmacological interventions do not seem to be specific on painful symptoms besides GAD.

In the last years, antiepileptic drugs have been increasingly investigated as a potentially effective pharmacological alternative in patients with GAD. Among these, agents like Gabapentin and Pregabalin present a specific efficacy over pain syndromes like neuropathic pain. Pregabalin, in particular, represents a new anxiolytic recently licensed for the treatment of GAD in Europe as well as an effective therapy in patients with diabetic peripheral neuropathy, postherpetic neuralgia, and adults with refractory partial-onset seizures. In addition it presents a predictable and linear pharmacokinetic profile, a prevalent renal excretion and no interactions with other anticonvulsants. Randomized, controlled trials indicate that Pregabalin, in doses ranging between 150 and 600 mg/day, is superior to placebo and as effective as Lorazepam, Alprazolam and Venlafaxine for the treatment of patients with moderate-to-severe GAD [2]. Of note, the onset of anxiolytic activity for Pregabalin appears within the first week of treatment, which is faster than that obtained with Paroxetine and Venlafaxine. Pregabalin does not provoke a clinically significant withdrawal response and has low potential for abuse and dependence, unlike other classes of medications used for the treatment of GAD. Given the well established effect of Pregabalin on painful syndromes and the frequent comorbidity between GAD and pain related conditions as well as the possible presentation of GAD with somatizations and painful symptoms, clinicians may consider the use of Pregabalin as a valid alternative therapy for their patients with GAD.

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SO 0803. Treatment of co-morbid pain with venlafaxine or desvenlafaxine

J.M. Germain

Wyeth Pharmaceuticals, Coeur Défense, Paris-la-Défense, France

Painful physical symptoms are common features of major depressive disorder [1,2]. It is also suggested that relapse into depressive episode are more common in patients with persistent chronic pain, making full symptoms remission difficult to achieve [3].

Although different neuroanatomical pathways are involved in the control of mood and pain, it is commonly accepted that deficiency in both serotonin and norepinephrine would affect both mood and pain [4]. Therefore the selective serotonin and noradrenaline reuptake inhibitor venlafaxine is expected to improve both depressive symptoms and painful physical symptoms. Main results with venlafaxine and recent therapeutic advances will be reviewed in this presentation.

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SO 0803. Treatment of co-morbid pain with milnacipran or duloxetine

M. Briley

NeuroBiz Consulting & Communication, Castres, France

The overwhelming majority of depressed patients suffer from co-morbid chronic pain. In addition chronic pain is a major risk factor for depression and suicidal behaviour. Not only do depression and chronic pain frequently co-exist but they probably result from a common neurobiological dysfunction at the level of the monoaminergic cell bodies in the basal ganglia. Indeed it appears legitimate to consider chronic pain as an integral symptom of depression alongside sleep disturbances, appetite changes, sexual dysfunction and suicidal behaviour.

Chronic pain, as modelled in animals, is significantly decreased by amitriptyline which inhibits both serotonin and noradrenaline reuptake. Similar effects are obtained with the serotonin and noradrenaline reuptake inhibitors (SNRI), milnacipran and duloxetine. Selective serotonin reuptake inhibitors

(SSRI), however, are only weakly active. An overview of animal and clinical studies in chronic pain has shown that dual-acting reuptake inhibitors were more active than selective NA reuptake inhibitors, which were, in turn, were more active than SSRIs. Similarly a meta-analysis of placebo-controlled studies of various antidepressants in the treatment of chronic lower-back pain concluded that dual action antidepressants were effective in reducing pain, whereas SSRIs were not.

Recently, a number of open and controlled clinical trials with the SNRIs, milnacipran and duloxetine, suggest that these compounds are effective in relieving a variety of chronic pain conditions. Although these effects may be due, in part, to an antidepressant action they are principally the result of a true analgesic effect and can be seen whether depression is present or not. In addition, duloxetine and milnacipran may also play a role in modulating neurogenesis and other neuroplastic changes in the central nervous system, possibly leading to more complete recovery in patients suffering from the symptoms of depression and chronic pain.

SO 09. Diagnosis, Treatment and Receptors are critical in patient recovery in mood and anxiety disorders**SO 0901. Misdiagnosis in Mood Disorders**

D. V. Sheehan

University of South Florida College of Medicine, USA

Major depressive disorder is the most common psychiatric disorder. The spectrum of bipolar disorders is also common in psychiatric practice. Yet these disorders are under-diagnosed, even in mental health settings. When clinicians suspect that their patient has a mood disorder, they not infrequently diagnose major depressive disorder, when the patient has a bipolar disorder. It is also not uncommon for patients to be diagnosed with schizophrenia, schizoaffective disorder or brief psychotic episode, when they have a mood disorder with psychotic features.

To some, these distinctions may appear to be an idle academic exercise. In both research and clinical settings these distinctions are of central research and therapeutic importance. In general, patients with major depressive disorder respond well to antidepressants. However, the evidence suggests that standard antidepressants have little significant benefit in the long term management of bipolar disorder. Indeed in some patients with bipolar disorder, the use of standard antidepressants can induce rapid cycling, perpetuate cycling behaviors and can even induce switches into mania and suicidal depression. In contrast, mood stabilizers are usually not helpful in the treatment of major depression, although they

may have some protective effect against future depressive episodes and suicidality.

In selecting patients for clinical trials, accurately diagnosing the mood disorder is essential to ensure a successful outcome. Diagnostic sloppiness in research studies can lead to bipolar patients being put into studies of major depression (because their symptoms may meet criteria for major depressive episode). Since such patients do not respond well to standard antidepressants, this miss-assignment can lead to a failed study, even when the drug is an effective antidepressant. Similarly, in drug development with new treatments, it is important to strive for diagnostic accuracy in our patient population, so we can accurately identify the patients who benefit or get worse.

The best way to achieve diagnostic accuracy in selecting patients for mood disorder studies and in clinical practice settings is the use of structured diagnostic interviews. Such structured diagnostic interviews can be implemented in less than 15 minutes.

With the existing diagnostic criteria for mood disorders there are several thousand permutations and combinations possible. It is difficult for the human brain to consistently compute such a large number of combinations with accuracy. This results in frequent misdiagnosis in mood disorders. It is likely in the future that there will be an increased use of computerized structured diagnostic interviews and laboratory tests to improve diagnostic accuracy in mood disorders.

SO 0902. Room for improvement in the treatment of generalized anxiety disorder

D.S. Baldwin

Clinical Neuroscience Division, University of Southampton, United Kingdom

Generalized anxiety disorder (GAD) is a common and debilitating medical condition, associated with significant social and occupational impairment, and is traditionally thought to run a chronic course, waxing and waning in severity. A range of pharmacological treatments for patients with GAD are available, including certain selective serotonin reuptake inhibitors (SSRI), the serotonin-noradrenaline reuptake inhibitors (SNRI) venlafaxine and duloxetine, some benzodiazepines, and the novel anticonvulsant and anxiolytic drug, pregabalin. The conventional neuroleptic trifluoperazine has been found efficacious in acute treatment and the second generation antipsychotic drugs risperidone and olanzapine have been found helpful in placebo-controlled augmentation studies in patients responding only poorly to initial treatment with an SSRI (Baldwin & Polkinghorn, 2005).

When treating patients with GAD, important considerations underlying treatment decisions include the overall efficacy of treatment, the time

before an apparent onset of action, the relief of both psychological and physical symptoms of anxiety, the ability to achieve symptomatic remission and to minimise symptom-related disability, efficacy in sustaining response over the long-term, and the cost-effectiveness of treatment. In addition, the nature of treatment-emergent adverse events, the safety of treatment in physically ill patients (as GAD is often comorbid with general medical conditions) and the risks of developing tolerance or experiencing troublesome discontinuation symptoms will all affect treatment choices.

This presentation will summarise current evidence base for the treatment of patients with GAD, highlighting those areas where there is room for improvement in optimising clinical outcomes.

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SO 0903. Treatments and their mechanisms of action in major depressive disorder

S. Montgomery

Imperial College School of Medicine, London, UK

Conventional SSRIs excluding escitalopram have been shown to be effective in treating MDD but have the disadvantage of working slowly and being only modestly effective in treating severe depression. The addition of noradrenaline reuptake to SSRIs (as in SNRIs) has produced some evidence of greater efficacy in severe depression with venlafaxine and milnacipran but does not result in fast action.

A more rapid response in depression than with SSRIs has been reported with amisulpiride and suggest that a dopaminergic approach may be useful. The recent placebo-controlled results with quetiapine, where rapid response is observed in both bipolar depression and unipolar depression, reinforce the need to consider different mechanisms of action to maximise response and speed of action.

SO 10. Treatment of the elderly

SO 1001. Treatment of insomnia in the elderly

J. Caron

Sepracor, Massachusetts, USA

Insomnia is a disorder of sleep initiation, sleep maintenance, or nonrestorative sleep that impairs daily function and causes daytime distress. Sufferers often become accustomed to this impaired level of functioning and may not seek care or report it to their healthcare provider. The elderly suffer disproportionately from insomnia, with prevalence rates of 20–50% (vs 9% to 15% in the general adult population). Sleep problems in elderly adults have been

linked to increased risk of accidents or falling (over and above the established risk between accidents/falls and sedative-hypnotic use) and nursing home placement. In addition, the elderly have unique treatment needs that pose challenges for clinicians, including the need to effectively treat sleep maintenance insomnia, which is the most frequently reported sleep disturbance in the elderly; the increase in comorbidities (which are often the cause of or contribute to their insomnia); the increased use of concomitant medications (raising the risk of drug-drug interactions); the increased sensitivity to the adverse effects of some drugs, particularly those with antihistaminic or anticholinergic properties. Data on the use of sleep agents in elderly patients, however, are very limited, and very few polysomnography (PSG) studies have been conducted.

Eszopiclone is a novel, single-isomer, nonbenzodiazepine, cyclopyrrolone agent, which has demonstrated efficacy in non-elderly and elderly adults with primary insomnia and comorbid insomnia. Two studies have been conducted in 460 patients 65–85 years of age, each lasting 2 weeks. Sleep was evaluated using patient reports of sleep, and one study also utilized PSG. The results indicated that eszopiclone 2mg was well-tolerated and improved measures of sleep using patient reports and PSG, including sleep onset, sleep maintenance, sleep duration, quality and depth of sleep compared with placebo. These improvements in sleep were accompanied by improvements in measures of daytime function (daytime alertness, ability to function, and sense of physical well-being), and a reduction in daytime napping. When data were stratified by age (65–75 and 75–85), similar results were seen for measures of safety and efficacy.

These studies represent the largest placebo-controlled, double-blind clinical trials of a nightly administration of a hypnotic in elderly patients diagnosed with primary insomnia. Most relevant for this patient population, eszopiclone significantly reduced measures of sleep maintenance symptoms (including WASO, wake time during sleep, and hourly cumulative wake time during sleep) and daytime napping, the primary complaints among elderly patients with sleep difficulties. These studies were limited to generally healthy, community dwelling elderly patients who received eszopiclone 2 mg for 2 weeks. Future studies of long-term eszopiclone treatment in elderly patients with insomnia and insomnia co-existing with other comorbid conditions are warranted.

SO 1002. Efficacy and Safety of Pregabalin for the Treatment of Generalized Anxiety Disorder in elderly patients

T.K. Murphy, S. Montgomery, E. Whalen
Pfizer Global Pharmaceuticals, Pfizer Inc, New York, USA

Objective: The prevalence of generalized anxiety disorder (GAD) among the elderly is 3.7% to 7.4%, which is on par with prevalence estimates of this disorder in young adults. A Phase III clinical trial was performed to evaluate the safety and efficacy of pregabalin in relieving the symptoms of GAD in patients ≥ 65 years of age. In several double-blind, placebo-controlled trials, pregabalin demonstrated efficacy in the treatment of GAD with a rapid onset of action (within the first week) and efficacy in improving both psychic and somatic anxiety symptoms. **Methods:** This was a multicenter, randomized, flexible-dose, placebo-controlled, double-blind, parallel-group trial. Enrollees were male or female outpatients ≥ 65 years of age who met the *DSM-IV* criteria for GAD as established by the Mini-Neuropsychiatric Interview and a psychiatrist. Patients had a total Hamilton Anxiety Rating Scale (HAM-A) score ≥ 20 at the screening and randomization, had a Mini-Mental State Examination of Folstein total score ≥ 24 , and were otherwise in good general health. Patients underwent an 8-week double-blind, flexible-dose (between 150 and 600 mg/d) treatment phase, including a 1-week titration period (50 to 150 mg/d). The primary efficacy assessment was change from baseline (last observation carried forward) in HAM-A total score.

Results: 273 patients were randomized and received study treatment. 77% of patients were women. Mean age at GAD onset was 56 years; mean age at enrollment was 72 years; mean duration of GAD was 17 years. On the primary outcome, pregabalin was significantly superior to placebo from week 2 through the end of double-blind treatment. There was also a significantly greater global improvement as measured by the CGI-I total score with pregabalin versus placebo. The most common adverse events (AEs) among pregabalin-treated patients were dizziness (20.3%), somnolence (13.0%), headache (10.2%), and nausea (9.0%). Most AEs were mild-to-moderate and self-limiting. Discontinuation rates due to AEs were 10.7% and 9.4% in the pregabalin and placebo groups, respectively.

Conclusions: Pregabalin, in doses of 150–600 mg/day, was effective in reducing the symptoms of GAD in patients aged 65 years and older, and was safe and well tolerated in this population. Pregabalin significantly improved both psychic and somatic symptoms of anxiety.

Supported by Pfizer Inc.

SO 1003. Treatment of Schizophrenia in the elderly

M. Eerdekens¹, L. Ford², C. Gassmann-Mayer², P. Lim², M. Kramer²

¹Johnson and Johnson Pharmaceutical Research & Development Turnhoutseweg, Beerse, Belgium

²Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, New Jersey, USA

Introduction: Older patients (≥ 65 years) are under-represented in current research data relating to the management of schizophrenia. As this population is increasing [1], more information pertinent to this population is required given the difficulty in extrapolating data from a younger population to guide treatment decisions for geriatric patients. Elderly patients are at increased risk of adverse effects, have high rates of additional comorbid illnesses, take more concomitant medications and are affected by changes in pharmacokinetic characteristics (resulting from alterations of absorption, distribution, metabolism and elimination). Moreover elderly patients with schizophrenia experience more severe movement disorder symptoms, have higher rates of tardive dyskinesia [2] and are more prone to orthostatic hypertension and anticholinergic adverse effects [3].

Methods: Data from a prospective double-blind 6-weeks trial in which patients (age ≥ 65 years) were randomised to the new psychotropic (paliperidone extended release (ER), flexibly dosed between 3 and 12 mg/day starting at 6 mg/day) and placebo (2:1 ratio) followed by an open-label extension period of 6 months will be presented.

Results: Patients ($N=114$) were predominately female (73%), mean age = 70 years (double-blind phase). During double-blind treatment, discontinuation rates due to adverse events were similar between groups (paliperidone ER: 7%, placebo: 8%), as were incidences of treatment-emergent adverse events (paliperidone ER: 67%, placebo: 71%) whereas serious adverse events occurred in 3% of the paliperidone ER- and 8% of the placebo-treated patients. Safety and tolerability results in the extension were consistent with the shorter-term results. Paliperidone ER treatment resulted in clinically meaningful improvements during double blind treatment: change in total positive and negative syndrome scale (PANSS) from baseline to endpoint was -14.6 (SD 14.6; paliperidone ER) versus -9.9 (SD 15.0; placebo); difference of LS means (SE): -5.5 (2.20); 95% CI: -9.85; -1.12.

Conclusion: Paliperidone ER (3–12 mg/day) treatment over a 30-week period was generally well tolerated and improved symptoms in elderly patients with schizophrenia.

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SO 1004. Pharmacokinetic influences on treatment of the elderly

P. Baumann

University Department of Psychiatry, CHUV, Prilly-Lausanne, Switzerland

Many factors contribute to the increased risk for adverse effects in psychogeriatric patients treated with antidepressants and/or antianxiety agents: pharmacoepidemiological studies show that these patients are frequently comedicated with other psychotropic drugs such as antipsychotics, anticonvulsants used as mood stabilizers, but also with somatic drugs. The presence of both somatic and psychiatric comorbidities results in the implication of several prescribers. Unfortunately, coordination between the prescribers may not be optimal and this contributes to increase the risk for adverse effects in a population, which is particularly sensitive to adverse effects (Green, *Am J Geriatr Pharmacother* 5 (2007) 31). Indeed, drug absorption, distribution, metabolism and elimination (ADME) may be altered in the elderly (Schwartz, *Clin Pharmacol Ther* 82 (2007) 87) and pharmacokinetic interactions may have particularly severe consequences (Spina and Scordo, *Drugs Aging* 19 (2002) 299). Most psychotropic drugs are substrates and/or inhibitors of cytochrome P-450. The increased knowledge about this enzymatic system allows a better understanding of underlying mechanisms responsible for pharmacokinetic interactions responsible for adverse effects. In this context, therapeutic drug monitoring represents a useful tool to optimise treatment, as many generally admitted indications apply for elderly patients (Baumann et al., *Pharmacopsychiatry* 37 (2004) 243): Lack of compliance, adverse effects despite the use of generally recommended doses, suspected drug interactions, combination treatment with a drug known for its interaction potential, patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease). On the other hand, there is a lack of experimental evidence as clinical pharmacological studies in elderly patients are relatively rare.

IFMAD Poster Abstracts

P 01. Impulsivity in bipolar patients with and without substance use

A. Afkhami^{1,2}, B. Daneshmand^{1,2,3}, M. Shekarian¹

¹Iran University Of Medical Sciences, ²Mental Health Research Center, Tehran Institute of Psychiatry, ³Iran Psychiatry Centre, Iran

Background: Substance abuse is present in most patients with bipolar disorder and associated with poor treatment outcome and increased risk of suicide and aggression. The objective of this study

is to compare the severity of impulsivity and its domains in bipolar patients with and without substance abuse.

Method: A total of 154 bipolar manic patients (90 men and 64 women; 77 with substance use and 77 with no history of substance use) who were attended a psychiatry centre consisted the sample. The patients first screened for a diagnosis of BID manic phase by SCID and those who met the inclusion criteria completed Barratt Impulsivity Scale (BIS11). BIS11 is a 30 item self-report questionnaire designed to measure impulsivity in three domains: motor, nonplanning and attentional impulsivity. A cut-off point of >66 indicates the severity of impulsivity.

Results: the BIS total score and domains scores were significantly different among two groups. Within bipolar-substance use group the heroin and cannabis users showed the highest scores in nonplanning and attentional impulsivity domains. **Conclusion:** The increased predisposition to impulsivity in bipolar patients with substance use may contribute to the decrement in treatment outcome and compliance and increased risk for suicide and aggression. Impulsivity may be a link between bipolar disorder and substance use.

Keywords: Impulsivity, Bipolar disorders, Substance abuse, Barratt Impulsivity scale

P 02. Quetiapine and classical mood stabilizers in the long-term treatment of bipolar disorder: a 4-year follow-up naturalistic study

A.C. Altamura¹, E. Mundo¹, B. Dell'Osso¹, G. Tacchini¹, M. Buoli¹, M. Serati¹, J.R. Calabrese²

¹Dept. of Psychiatry, University of Milan, IRCCS Fondazione Ospedale Maggiore Policlinico Mangiagalli, Milan, Italy; ²Mood Disorders Program, Department of Psychiatry, Case Western Reserve University, University Hospitals of Cleveland, Cleveland, Ohio, USA

Background: Evidence on the use of quetiapine in the long-term treatment of Bipolar Disorder (BD) is limited¹ with no studies comparing the efficacy of different mood stabilizers in preventing the recurrence of both full-syndromal and sub-threshold mood episodes in BD. The primary aim of this naturalistic study was to compare the effectiveness of quetiapine and classical mood stabilizers, as mono- or combination therapy, in the long-term treatment of BD.

Methods: 289 DSM-IV BD I ($n=119$) or BD II ($n=170$) patients, treated and followed up between June 2001 and June 2005 were studied. Mood stabilizers were chosen by the treating psychiatrists on the basis of their clinical judgement. The sample was sub-divided into 7 treatment groups: quetiapine ($n=41$), lithium ($n=39$), valproate ($n=73$), lamo-

trigine ($n=31$), other therapies ($n=57$), quetiapine plus lithium ($n=25$), and quetiapine plus valproate ($n=23$). Throughout the 4-year follow-up period, patients were assessed monthly or whenever a recurrence occurred by the administration of HAM-D-21 and of the YMRS, in order to assess the presence/absence of the recurrence of any major or sub-threshold mood episode. Primary outcome measures were the duration of euthymia (i.e., survival time) and the cumulative proportion of subjects who maintained euthymia. Kaplan-Meier survival analyses were done to tabulate and compare the differences in survival distributions across the different treatment groups (Log-rank Mantel-Cox test).

Results: The combined treatment with quetiapine plus lithium was more effective overall in maintaining euthymia, with particular respect to the prevention of the recurrence of both major and sub-threshold depressive episodes. In addition, quetiapine monotherapy was effective in preventing the recurrence of major depressive episodes.

Conclusion: If the results from this study will be replicated, there will be important implications for the use of quetiapine in the long-term treatment of BD.

Keywords: Bipolar Disorder, mood stabilizers, long-term treatment, effectiveness, quetiapine, sub-threshold episodes.

P 03. ADOKOT study: Safety of sodium divalproate (Dépakote®) in adolescents suffering from bipolar disorder in manic, mixed or hypomanic phase

J.M. Azorin¹, D. Cohen², H. Caci³, R. P. Garay⁴, A. Hameg⁵

¹Hôpital Sainte-Marguerite, Marseille, ²School of Medicine, Hospital le Pitié-Salpêtrière, ³Hôpital Archet II, Nice, ⁴EA2381, University Paris 7, Paris, ⁵Sanofi-Aventis-France, Paris, France

Several studies have shown that thymoregulators (lithium, sodium divalproate) and atypical antipsychotics (olanzapine) are efficient to treat manic episodes in adolescents with bipolar disorder, but none of these compounds is still approved for this therapeutical indication in Europe. The ADOKOT study was designed to evaluate the clinical and biological safety of sodium divalproate (Dépakote®) in adolescents suffering from bipolar disorder in manic, mixed or hypomanic phase (DSM IV). Of 200 programmed bipolar patients, 24 patients, aged 15.1 ± 1.7 years old, were included in the study (10 females, 14 males). Patients were initially treated with sodium divalproate 500 mg/day, followed by a stepwise increase of 250 mg/day to reach an optimum dose in about one week (not exceeding 30 mg/kg/day), for a total treatment duration of 6 months. Primary endpoint was safety, as assessed by clinical examination and biological data. Twenty-three

patients exhibited at least one adverse event during the study (2 patients interrupted treatment). Of these, 14 patients were considered as having a treatment-related undesirable event. Headaches and digestive disorders, commonly known side effects of sodium divalproate, were the most commonly listed events. Six patients exhibited a serious event: 2 patients attempted suicide and 4 patients presented symptoms related to their bipolar disorder (depression $n=1$, mania or hypomania $n=3$). Of these latter, only one of the 6 serious adverse events was considered as treatment-related. Patients tended to increase weight, without changes in cardiovascular parameters. Moderate hyperammonemia (without alteration of biochemical markers of liver function) was the most common biochemical disorder (8 patients). Finally, one patient had a reduction in fibrinogen levels. In conclusion, the safety profile of sodium divalproate in adolescent bipolar patients seems not different from that previously observed in adult patients, but, due to the small number of studied patients, further investigation is required to confirm this point.

P 04. Survival rates of maintenance treatment with Venlafaxine ER in patients with somatic symptoms

W. Bahk, H. Seo, Y-S. Woo, T. Jun, J. Chae
Department of Psychiatry, College of Medicine, the Catholic University of Korea, Seoul, South Korea

Aim: Medically unexplained physical symptoms were predominant complaints of depressive patients in clinical settings. The objective of this study was to evaluate the efficacy of venlafaxine ER, which also have the effects on both serotonin and norepinephrine, in depressive patients with somatic symptom.

Method: The subjects were recruited from outpatients who had been treated for depression with venlafaxine ER. They were divided into two groups, whether they represented somatic symptoms as their chief complaints (somatic group) or not (non-somatic group). Addition to this, they also divided into two groups according as they met the criteria of multisomatoform disorder (DSM-IV, Primary Care Version) or not. The duration from the time initiate venlafaxine ER to the point when medication was changed due to recurrence of any symptoms and side effects was assessed and compared by survival analysis in two groups.

Results: Sixty four patients fulfilled the inclusion criteria of this study, and 39 patients of them divided to 'somatic group' and the other 25 patients to 'non-somatic group'. Survival rates of maintenance treatment in somatic group was significantly higher than non-somatic group (log rank test $p=0.033$), and the mean duration of maintenance treatment in somatic group was 41.5 ± 3.38 weeks and that of non-somatic

group was 26.0 ± 4.95 weeks. When the somatic symptoms were classified by their frequency, palpitation and headache were most frequent ($n=17$, 43.6%), and dyspeptic complaint, dizziness and shortness of breath were following in their order. When the subjects were classified by the criteria of multisomatoform disorder, there was no significant difference between the two groups (log rank test $p=0.314$).

Conclusion: In the present study, the treatment with venlafaxine ER was maintained longer in depressive patients with somatic complaints, and it suggested the efficacy of venlafaxine ER on somatic symptoms of depressive patients. To confirm our result, well controlled trial are needed in the future.

P 05. Relationship between predominant episode and clinical features in Bipolar I Disorder

W. Bahk, H. Seo, Y. Woo, T. Jun, J. Chae
Department of Psychiatry, College of Medicine, the Catholic University of Korea, Seoul, South Korea

Aims: In this study, we present a comparison of bipolar patients with predominance of depressive episodes and with predominance of manic episodes in clinical implication.

Methods: The recruitment was conducted within inpatients who had received psychiatric treatment for bipolar I disorder. The number and polarity of past episodes were assessed, and subjects were divided to depressive or manic episode predominant groups. These groups were defined as the number of one episode was greater than the other episode at least by two. The patients who did not meet the criteria for predominant group and who have shown any mixed and ambiguous episodes were excluded. The data were analyses using Student's t-tests and chi-square test.

Results: Forty nine subjects were classified as depressive episode predominant group (depressive episode group) and twenty eight subjects as manic episode predominant group (manic episode group). Psychotic symptoms were more prominent in depressive episode group significantly ($X^2=5.84$, $df=1$, $p=0.016$). 89.4% ($n=44$) subjects of depressive episode group showed depressive episode as first episode, and 92.9% ($n=26$) of manic episode group experienced manic episode as first episode ($X^2=50.61$, $df=1$, $p<0.001$). In the comparison of past year highest GAF score and total number of episodes, significant differences were found between two groups ($t=2.48$, $df=75$, $p=0.015$; $t=-2.63$, $df=32.08$, $p=0.040$).

Conclusion: The type of onset episode appears related to predominant episode in our study. And patients with predominant depressive episode related to psychotic symptoms and patients with predominant

manic episode related to more recurrent episodes and lower functioning.

P 06. Resolution of sexual dysfunction during acute treatment of major depression with Milnacipran

D. Baldwin¹, R. Moreno², M. Briley³

¹Clinical Neuroscience Division, School of Medicine, University of Southampton, Southampton, UK, ²Mood Disorders Unit-Department of Psychiatry, University of São Paulo Medical School, São Paulo, Brazil, ³Neurobiz, Castres, France

Depression is associated with impairment in sexual function and satisfaction and most classes of antidepressant drugs can exert adverse effects on sexual function. The complex relationship between depression and sexual function makes evaluation of the net outcome of antidepressant treatment difficult (improved sexual function through a beneficial effect but sexual dysfunction through adverse effects). Cultural differences can also complicate assessment of sexual function.

The sexual function and enjoyment questionnaire (SFEQ) was developed as an attempt to assess sexual function in men and women and to detect changes due to altered clinical state and treatment emergent side-effects. The SFEQ was employed to evaluate the effects of the serotonin-noradrenaline reuptake inhibitor, milnacipran, in the treatment of major depression in two investigations: a 12-week open study in Brazil and a 6-week controlled study in Europe (Belgium, France, Germany, Italy, Netherlands, Portugal, Spain, Switzerland, United Kingdom). Data was analysed from all patients who provided replies to all SFEQ questions at all time points (Brazilian study 64 women and 16 men; European study 64 women and 33 men).

In both studies mean Hamilton Depression Rating (HAMD) scores decreased progressively. At end-point 61% of patients (Brazil) and 78.4% (Europe) were responders (i.e. >50% reduction of baseline HAMD score), and 17.5% (Brazil) and 18.6% (Europe) were in remission (i.e. HAMD <8 for at least 2 weeks). At study end-point all SFEQ items showed improvements in sexual function in both studies: 60% of patients in the Brazilian study and 56% in the European said their sexual desire was as great as or better than it had been before their depressive episode.

Milnacipran appears to improve sexual function in parallel with other symptoms of depression with no lasting tendency to aggravate any aspects of sexual dysfunction. The SFEQ is a sensitive instrument for measuring changes in sexual function and does not appear affected by cultural differences as shown by similar findings in Latin American and European populations.

P 07. Results from a phase III study of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalised anxiety disorder

B. Bandelow¹, J. Bobes², A. Ahokas³, I. Eggens⁴, S. Liu⁵, M. Brecher⁵

¹Department of Psychiatry and Psychotherapy, University of Goettingen, Goettingen, Germany,

²Department of Psychiatry, University of Oviedo, Asturias, Spain, ³Mehilainen Clinic, Helsinki, Finland, ⁴AstraZeneca R&D, Södertälje, Sweden,

⁵AstraZeneca Pharmaceuticals, Wilmington, USA

Background: To evaluate efficacy and tolerability of once-daily quetiapine XR (extended release) in patients with generalised anxiety disorder (GAD).

Methods: 10-week (8-week active treatment, randomised phase; 2-week post-treatment drug-discontinuation/tapering phase), multicentre, double-blind, randomised, parallel-group, placebo- and active-comparator study (D1448C00011). Patients were randomised to quetiapine XR 50mg/day, 150mg/day, paroxetine 20mg/day or placebo. Primary efficacy outcome was change from baseline to Week 8 in HAM-A total score. Other key outcomes included: change in HAM-A total score from baseline to Day 4, HAM-A response ($\geq 50\%$ decrease from baseline) and remission (HAM-A total score ≤ 7) at Week 8. Adverse events (AEs) were recorded throughout the study.

Results: 873 patients were randomised: 221 quetiapine XR 50mg/day; 218 quetiapine XR 150mg/day; 217 paroxetine; 217 placebo. Mean HAM-A total score (overall baseline mean, 26.98) was significantly reduced at Week 8 by quetiapine XR 50 mg/day (-13.95 , $p < 0.05$), quetiapine XR 150 mg/day (-15.96 , $p < 0.001$) and paroxetine (-14.45 , $p < 0.01$) versus placebo (-12.30). Statistically significant separation from placebo (-2.90) in HAM-A total score was observed at Day 4 for quetiapine XR 50mg/day (-4.43 , $p < 0.001$) and 150 mg/day (-3.86 , $p < 0.05$) but not paroxetine (-2.69 , $p = 0.6$).

At Week 8, response rates were significantly higher for quetiapine XR 50mg/day (62.6%, $p < 0.05$), 150mg/day (70.8%, $p < 0.001$) and paroxetine (65.9%, $p < 0.001$) versus placebo (52.1%). Remission rates were significantly higher for quetiapine XR 150mg/day (42.6%, $p < 0.01$) and paroxetine (38.8%, $p < 0.05$) versus placebo (27.2%).

During Weeks 1–8 the most common AEs ($> 10\%$) were: dry mouth (15.9, 25.7, 9.8, 6.0%), somnolence (21.8, 25.2, 11.2, 4.6%), fatigue (15.0, 16.5, 9.3, 3.7%), dizziness (11.8, 15.6, 13.5, 6.0%), headache (16.4, 12.4, 17.2, 18.0%) and nausea (7.7, 6.4, 20.5, 7.4%) with quetiapine XR 50mg/day, 150mg/day, paroxetine and placebo, respectively.

Conclusions: Once-daily quetiapine XR at 50mg/day and 150mg/day is effective and well tolerated in

GAD, with onset of response as early as Day 4. Paroxetine was also well tolerated and effective compared with placebo, although onset of response was not observed by Day 4.

P 08. Duloxetine in depressed alcoholic patients

E. Batlle¹, T. Fernández¹, V. Gironès², J. Martínez², I. Rivas³, C. Romero³

¹Hospital Mataró, Psychiatry Service, Mataró,

²Hospital Calella, Drug Dependence Service, Calella, ³Centre Delta, Badalona, Spain

Alcoholic patients with dual pathology show a poorer course and a lower treatment adherence. Duloxetine is a serotonin – noradrenaline reuptake inhibitor that differs from other antidepressants by virtue of its balanced potency on both neurotransmitter systems. This drug could therefore be effective for the treatment of patients showing both alcohol dependence and depressive disorders with severe behavioural clinical symptoms and who have difficulties to comply with drug treatment and clinical follow-up.

Objective: The purpose of this study is to assess the efficacy and safety of duloxetine for the treatment of depressed patients with comorbid alcohol dependence. The effect of duloxetine treatment on alcohol craving and use are also researched.

Methods: An observational outpatient multi-centre study, was carried-out in 40 patients with criteria for major depressive disorder, dysthymia or adaptative disorder, and additionally diagnosed of alcohol dependence, that were attended in drug abuse specialized centres and received duloxetine for almost 12 weeks. Demographic items, clinical scales and self-assessed levels of alcohol craving and frequency of consumption were used to assess effectiveness.

Results: Information was collected on a total of 40 patients, 32,5% women and 67,5% men, with a mean age of 45,9 years. All patients had been diagnosed of alcohol dependence, and depressive disorders (72,5% major depressive disorder, 20% dysthymia and 7,5% adaptative disorder). The mean daily dose of duloxetine was 60 mg at 4 weeks, 70,5 mg at 8 weeks, and 74,2 mg at 12 weeks (range 60 to 120 mg). A decrease was seen in the mean scores of the Hamilton Depression Scale (from 19,5 at baseline to 8,1 at 12 weeks). The mean levels of craving showed a gradual decrease (from 6.9 at baseline to 3.1 at 12 weeks). The frequency of alcohol consumption decreased and the percentage of abstainers gradually increased (from 5% at baseline to 57,5% at 12 weeks).

Conclusion: These results suggest that duloxetine could be an safe and effective drug treatment for depressed patients with comorbid alcohol dependence.

P 09. Results from a phase III study of extended release quetiapine fumarate (quetiapine XR) as add-on to antidepressants in patients with major depressive disorder (MDD)

M. Bauer¹, H.W. Pretorius², W. Earley³, P. Lindgren⁴, M. Brecher³

¹Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Dresden, Germany, ²Department of Psychiatry, University of Pretoria & Weskoppies, Hospital Pretoria, South Africa, ³AstraZeneca Pharmaceuticals, Wilmington, USA, ⁴AstraZeneca R&D, Södertälje, Sweden

Background: To evaluate the efficacy and tolerability of quetiapine XR (extended release) once-daily adjunctive to antidepressant therapy versus antidepressant alone in patients with MDD showing an inadequate response to antidepressant treatment.

Methods: 6-week, multicentre, randomised, double-blind, parallel-group study (D1448C00007). Patients with an inadequate response to antidepressant treatment (mainly SSRIs/SNRIs) were randomised to receive quetiapine XR (150 or 300mg/day) or placebo as add-on therapy to existing treatment. Primary endpoint: change from randomisation to Week 6 in MADRS total score. Secondary variables included: MADRS response ($\geq 50\%$ reduction in score from randomisation) and remission (MADRS total score ≤ 8) rates and change from randomisation to Week 6 in HAM-D and HAM-A. AEs were recorded throughout the study.

Results: 493 patients were randomised: 167 quetiapine XR 150mg/day; 163 quetiapine XR 300mg/day; 163 placebo. Mean MADRS, HAM-D and HAM-A total scores at randomisation were 28.4, 24.6 and 20.8, respectively.

Mean change in MADRS total score from randomisation to Week 6 was statistically significant ($p < 0.01$) for quetiapine XR 150mg/day (-15.26) and 300mg/day (-14.94) vs placebo (-12.21). Separation from placebo in MADRS total score was apparent from Week 1 ($p < 0.001$) for both quetiapine doses. At Week 6, 55.4%, 57.8% ($p < 0.05$) and 46.3% patients achieved MADRS response and 36.1% ($p < 0.05$), 31.1% and 23.8% achieved remission with quetiapine XR 150, 300mg/day and placebo, respectively. Quetiapine XR 150 and 300mg/day reduced HAM-D total scores from randomisation to Week 6 (-13.81 , $p < 0.001$ and -13.56 , $p < 0.01$, respectively vs placebo [-11.13]). HAM-A total scores were reduced from randomisation with quetiapine XR 150mg/day (-10.27 , $p < 0.01$) and quetiapine XR 300mg/day (-9.70 , $p < 0.05$) vs placebo (-7.92).

The most common AEs overall (%) were dry mouth (20.4, 35.0, 6.8), somnolence (16.8, 23.3, 3.1), fatigue (13.2, 14.7, 3.1), dizziness (11.4, 9.2, 7.5)

and headache (9.0, 7.4, 9.9) for quetiapine XR 150, 300mg/day and placebo, respectively.

Conclusion: In patients with MDD with an inadequate response to antidepressant treatment, adjunctive quetiapine XR at 150mg/day and 300mg/day was effective and well tolerated.

P 10. Clock gene polymorphism RE1801260 biases response to light treatment after sleep deprivation

F. Benedetti, L. Lietti, B. Barbini, C. Lorenzi, E. Marino, M. Cigala Fulgosi, A. Pontiggia, S. Dalla-spezia, C. Colombo, E. Smeraldi
Scientific Institute and University Vita-Salute San Raffaele, Department of Neuropsychiatric Sciences, Milan, Italy

Background: The rapid but transient effects of total sleep deprivation (TSD) can be sustained over time by combined and subsequent light therapy (LT). recent findings suggest that timing of morning LT is crucial to maximize response, with a 2-hours phase advance of the natural exposure to morning light as the optimal time for treatment. CLOCK 3111 T/C SNP (rs1801260) gene polymorphism is known to influence the morningness/eveningness and the phase and duration of night sleep in bipolar patients. **Methods:** Forty-six patients affected by bipolar depression were administered three consecutive TSD cycles followed by exposure to morning LT given early (in order to phase-advance exposure to morning light) or at 11 a.m. CLOCK rs1801260 was genotyped.

Results: Timing of morning light after repeated TSD influenced the therapeutic effect of LT depending on CLOCK rs1801260 genotype. The C allele, which is known to be associated with higher eveningness and later sleep onset and morning awakening, was here associated with a better effect of early morning LT in responders to TSD, while the T allele was not.

Conclusions: Results are consistent with previous findings showing that phase advance of the activity-rest rhythm is a correlate of response to combined TSD and LT, and suggest that individual characteristics of the biological clock.

P 11. Homeostatic and allostatic response to sleep deprivation in bipolar depression

F. Benedetti, M. Cigala Fulgosi, C. Gavinelli, B. Barbini, C. Colombo, E. Smeraldi
Scientific Institute and University Vita-Salute San Raffaele, Department of Neuropsychiatric Sciences, San Raffaele Turro, Milan, Italy

Background: Sleep deprivation (SD) is a well confirmed antidepressant treatment. Nevertheless, some

patients show only partial clinical improvement to SD. In the light of recent findings about the role of the biological clock in mood disorders, we hypothesized that responders and non-responders could differ in some parameters of the sleep-wake rhythm during treatment.

Methods: With actigraphic measurement here we studied sleep-wake parameters in twenty-seven inpatients (10 male/17 female) affected by bipolar depression and administered three consecutive SD cycles associated with daily LT exposure.

Results: Non-Responder showed a sleep pattern that could be indicative of a homeostatic response to acute sleep loss, with a progressive sleep need and longer and deeper sleep after the SD nights in respect to baseline and to responders, who showed only a modest increase in sleep duration after SD. Moreover, during the wake therapy non responders showed an higher numbers of naps than responders.

Conclusions: A possible interpretation of these findings is that the allostatic load linked with SD had a direct effect on the sleep-wake regulatory system, with non responders showing a homeostatic reaction, and responders an allostatic adaptation to sleep loss. These differences could be due to the individual characteristics of the biological clock, including allelic variants of the clock genes.

P 12. Stressful life events bias neural correlates of emotional processing in bipolar disorder

F. Benedetti, D. Radaelli, A. Bernasconi, S. Dalla-spezia, V. Unterhofer, C. Colombo, A. Falini, G. Scotti, E. Smeraldi
Scientific Institute and University Vita-Salute San Raffaele, San Raffaele Turro, Milan, Italy

Aggressiveness and high levels of conflict in the family environment are associated with a high risk of developing impulsiveness, antisocial behaviour, depression and suicide.

In early childhood, humans started to develop a specific ability to monitoring the environment and to detect potential threats. Neural networks, involving amygdala are activated when a new or unexpected element is detected in the environment.

The development of this neural system is influenced by family environment. Different studies suggest that this network is abnormally activated in bipolar patients.

Aim: Studying influence of stressful life events on neural responses to an emotional task in a sample of depressed patients.

Method: A 3.0 Tesla fMRI acquisition was used to study 13 bipolar depressed patients and 6 healthy controls. The cognitive activation paradigm was

based on a go/no-go task. Images representing facial expressions were randomly presented to the subjects. Stressful life events were assessed using the Risky Families Questionnaire RFQ (Taylor, 2004).

Results: In bipolar depressed patients we find a direct correlation between neural activity and RFQ score in perigenual cingulate cortex.

In healthy controls a direct correlation between activity and RFQ was detected in dorsolateral prefrontal cortex.

Conclusions: In subgenual cingulate patients affected by mood disorder show volume reduction and hyperactivity, in the same region higher activity is associated with higher RFQ score. In healthy subjects, stressful life events directly correlate with dorsolateral prefrontal cortex activity, and our results then suggest that the emotion management process after an higher stressful charge needs an higher activation of dorsolateral-prefrontal cortex.

P 13. A VNTR Polymorphism in hPER3 Gene Influences clinical characteristics of bipolar disorder

F. Benedetti, S. Dallaspazia, C. Lorenzi, A. Pirovano, C. Colombo, Enrico Smeraldi
Scientific Institute and University Vita-Salute San Raffaele, Department of Neuropsychiatric Sciences, San Raffaele Turro, Milan, Italy

Disregulation of circadian system is suspected to be involved in the pathogenesis of Bipolar Disorder (BD).

Human period 3 gene (PER3) is a member of the circadian period gene family. A polymorphism in the exon 18 of this gene, which consists in a domain composed by 4 or 5 tandem repeats of 54 bp, was found to be associated in diurnal preference, sleep structure and waking performance in healthy subjects. Moreover, it may be linked with circadian rhythm disorders such as delayed sleep phase syndrome. Nievergelt and colleagues found that haplotypes in PER3 were significantly associated with BD via single-gene premutation tests.

In order to investigate the possible influence of the variable number tandem repeat (VNTR) exon 18 PER3 polymorphism on clinical characteristic of BD, we studied 84 consecutively admitted inpatients affected by BD type I. Genotyping of exon 18 PER3 was performed for each patients.

One-way analysis of variance with genotype as independent variables showed the significant effect of genotype on the age of onset ($F = 3.35$; $p = 0.039$): PER5/5 individuals had an earlier onset than PER 4/5 individuals and PER 4/5 subjects had an earlier onset than PER 4/4 carriers.

A multiple regression analysis showed that patients with PER35/5 genotype, compared to PER34/4, had significantly better predictability for having a

lower percentage of manic episodes during the duration of illness ($b = -0.236$; $p = 0.042$).

PER3, like other genes of the molecular clock, influences clinical characteristic of BD. This is ulterior evidence of the circadian system involvement in the pathogenesis of BD.

P 14. Bipolar disorder and schizophrenia influence neural responses in amygdala and anterior cingulate to emotional faces

F. Benedetti, S. Poletti, D. Radaelli, S. Dallaspazia, A. Bernasconi, C. Colombo, R. Cavallaro, A. Falini, G. Scotti, E. Smeraldi
Scientific Institute and University Vita-Salute San Raffaele, San Raffaele Turro, Milan, Italy

Bipolar disorder (BD) and schizophrenia are associated with abnormalities in the way emotional stimuli are perceived, responded to, and stored in memory. Both disorders show abnormalities in BOLD signal in the amygdala and in the anterior cingulate during emotional tasks. The amygdala and the anterior and posterior cingulate, forms part of an extended network involved in the regulation of emotions.

The aim of our study is to investigate whether there is a common deficit in amygdala and anterior cingulate in the major disorders like BD and schizophrenia. A Philips Intera 3.0 Tesla was used to study 10 bipolar, 10 schizophrenic patients and 10 healthy controls. The cognitive activation paradigm was based on a go/no-go task. 12 different images representing facial expressions, 6 of each gender and affect (angry or afraid), were randomly presented to the subjects during the fMRI acquisition.

One way analysis of variance shows differences in the right amygdala (voxel coordinates 24, -10, -10) and in the bilateral anterior cingulate. Schizophrenic patients showed a greater activation in right amygdala compared to both bipolar and healthy subjects. Bipolar patients showed a smaller activation compared to the schizophrenic group but a greater one compared to the control group. In the cingulate the schizophrenic group showed a greater activation compared to the control and the bipolar group, the last one showed a smaller activation compared to both groups.

The results provide a possible neural correlate of a disturbance in core emotional processing common to major psychoses.

P 15. The effect of repetitive Transcranial Magnetic Stimulation

J. Chae¹, S. Lee², K. Baek³, J. Jeong³

¹The Catholic University of Korea, Seoul, ²Inje University, Koyang, ³Korea Advanced Institute of Science and Technology, Daejeon, South Korea

Fear memory extinction, a reduction in learned fear induced by repetitive exposure to conditioned fearful stimuli, is thought to be mediated by synaptic modifications in the medial prefrontal cortex (mPFC) and the amygdala. Neuronal activity in the infralimbic region (ventral part of the mPFC) markedly increased during recall of long-term extinction memory, and electrical stimulation to these neurons reduced fear response in the extinction phase and enhanced extinction learning. Transcranial magnetic stimulation (TMS) paired with trauma-related cues is suggested for treatment of exaggerated fear memory (i.e. post-traumatic stress disorder, PTSD), yet modulation effect of TMS on extinction memory is still unclear. This study aims at examining if TMS affect extinction learning of rats when paired or unpaired with conditioned tone (i.e. trauma-related cue). 24 hours after fear conditioning, rats received 10-Hz repetitive TMS during extinction learning paired ($n=7$) and unpaired ($n=6$) with conditioned tones, respectively. We found that not only paired but also unpaired TMS exhibited reduction in fear response after 15 trains of TMS ($p<0.05$), and that this enhanced extinction was still prominent on the next day ($p<0.01$), which is different from electrical stimulation. This observed long-term effect of TMS on extinction learning suggests that TMS may be able to augment synaptic potentiation possibly in the prefrontal cortex and/or the amygdala, possibly involved in extinction memory. This study suggests that TMS can be combined with the exposure therapy, a therapeutic intervention inspired from fear extinction, to treat dysregulated fear memory related condition such as PTSD.

P 16. Stress and alcohol

G. Danevski, P. Dimitrijevska

Psychiatric Hospital Skopje, Skopje, Macedonia

The term stress often is used to describe the subjective feeling of pressure or tension. However, the stress response is a complex process, the association between alcohol consumption and stress is more complicated still. Some studies of the correlation of stress and alcoholism show that many factors affect the incidence of chronic drinking and alcoholism as a response to stress, namely the genetic determinants of drinking, the individual attitude towards drinking before the stressful events, subjective expectations considering the effect of alcohol on stress, the intensity and type of the stress factor, and the availability of social support in alleviating the consequences of stressful effect. Furthermore, the studies show that the intense stress can cause the increased drinking if the better solutions are missing, if alcohol is available and if the person believes that alcohol would help reduce the stress.

The aim of this study was to investigate the consumption of alcohol and to determine the causes of such behavior and the disturbances connected with it.

In our investigation were included 64 patients treated at the Department of General and Forensic Psychiatry, Psychiatric Hospital Skopje, in the period from 2000 to 2005 under the diagnosis of Alcoholism.

All the patients were male and diagnosed according to DSM IV diagnostic criteria.

The results show that patients also fulfilled, along the basic diagnosis of stress, the diagnostic criteria for alcoholism (23,8%), depression (22,6%), permanent personality disorders (3%), psychotic disorder (1,8%), depression and alcoholism (1,2%).

In the group of patients fulfilling the diagnostic criteria for stress and alcoholism, 81,8% of them did not consume alcoholic drinks before the stress.

The results of our investigation point to a high correlation between stress and alcohol dependence.

In conclusion we can say that alcoholic dependence is one of the greatest and most untoward problems appearing in patients with stress. Namely, addiction complicates the course of the disease, and the negative effects upon treatment and rehabilitation.

P 17. Consultation-liaison psychiatry: managing suicide attempters

J. Del Río Vega, R. Fernandez Garcia-Andrade

Hospital Clínico Universitario San Carlos, Madrid, Spain

The present study examines the therapeutic approach to patients who have been admitted to hospital with medical, traumatic or surgical injuries due to a serious suicide attempt.

Method: A sample was taken of 48 suicide attempters (34 male, 14 female) who were being treated as inpatients in the Hospital Clínico Universitario San Carlos in Madrid. The sample patients were assessed by means of a partly structured psychiatric interview. For each one of the patients, the seriousness of attempt (according to the actual risk of dying and according to the Beck Suicidal Intent Scale), the comorbidity of mental disorders (CIE-10) and the therapeutic approach were all assessed.

Results: The majority of 32 patients who had made a high-risk attempt, presented emotional disturbance of a depressive nature, had symptoms of substance abuse or were diagnosed as suffering from a personality disorder. Only 8 (25%) had to be referred to a psychiatric unit for further treatment. Out of the 16 patients who had made a not too serious or moderately serious attempt, 10 presented symptoms of depression and 8 of them (50%) required a transfer to psychiatric ward.

Conclusion: the therapeutic approach to suicide attempters is largely determined by the co-morbidity of mental disorders rather than the seriousness of the attempt.

P 18. Social and occupational functioning in patients with partial or complete remission of a major depressive disorder episode

H. Delgado-Cohen¹, I. Romera¹, V. Perez², J.M. Menchón³, P. Polavieja¹, B. Yruretagoyena¹, I. Gilaberte¹

¹Clinical Research Department, Lilly Spain, ² Department of Psychiatry, Hospital de Sant Pau i de la Santa Creu, Barcelona, ³Department of Psychiatry, Hospital de Bellvitge, Barcelona, Spain

Objective: Evaluation of differences in social and occupational functioning between patients in partial remission (PR) and patients in complete remission (CR) of a Major Depressive Disorder (MDD) episode.

Methods: This is a 6-month multi-center, prospective, case-control study ($N=278$). Patients in PR (HAMD-17 score >7 and 15 or less) of a MDD episode (DSM IV-TR) were matched by age, gender and area with patients in CR (HAMD-17 score of 7 or less). All patients had been on antidepressant treatment for 12 weeks and no longer met criteria for MDD. Functioning was assessed by means of the Social and Occupational Functioning Assessment Scale (SOFAS).

Results: Mean (SD) patient age was 50.5 (14.5) years and 77% were female. At baseline HAMD-17 mean (SD) score was 12.0 (2.1) for PR group and 4.2(1.8) for CR group; and partial remitters showed greater impairment in social and occupational functioning than complete remitters (63.2 ± 12.4 vs. 80.7 ± 10.5 , respectively; $p < .0001$) who exhibited normal functioning (SOFAS mean score = 80 or more). After six months the difference in functioning remain significant between groups (76.2 ± 12.3 PR vs. 84.6 ± 9.3 CR; $p < .0001$) and a significantly lower percentage of partial remitters exhibited normal functioning (46.8% PR vs. 76.9% CR; $p < .001$). Partial remitters showed a greater improvement in HAMD-17 score (mean change; -4.8 ± 4.56 PR vs. -0.31 ± 3.36 CR; $p < .001$) of whom 59.4% achieved remission. Social and occupational functioning and depression severity were highly inversely correlated (Pearson $r = -0.62$). Predictive factors for achieving normal functioning were: being in complete remission of a MDD episode (Odds Ratio = 6.25) and exhibiting an improvement in HAMD-17 (Odds Ratio = 1.34). In addition, partial remitters reported three times more workplace absenteeism than complete remitters (63 vs. 20 days; $p < .001$).

Conclusions: Collectively study findings support that patients achieving only partial remission of a MDD episode have greater residual impairment in social and occupational functioning and an increase in total costs due to workplace absenteeism.

P 19. Optimal cutoff point to define remission by the Hamilton rating scale for depression according to normal social and occupational functioning

H. Delgado-Cohen¹, I. Romera¹, V. Perez², J.M. Menchón³, P. Polavieja¹, B. Yruretagoyena¹, I. Gilaberte¹

¹Clinical Research Department, Lilly Spain, ² Department of Psychiatry, Hospital de Sant Pau i de la Santa Creu, Barcelona, ³Department of Psychiatry, Hospital de Bellvitge, Barcelona, Spain

Background: Remission describes a state of minimal to no symptoms and the return to normal functioning and it is defined on the Hamilton Rating Scale for Depression (HAMD-17) as a cutoff score of 7 or less.

Objective: To explore the optimal cutoff point to define remission by the HAMD-17 according to normal social and occupational functioning.

Methods: This is a post-hoc analysis of a 6-month multi-center, prospective study ($N=292$). We examined the sensitivity and specificity of the HAMD-17 as a measure of normal functioning (SOFAS score = 80 or more) to obtain the optimal cutoff point that predicts a normal functioning.

Results: Mean (SD) patient age was 50.5 (14.5) years and 77% were female. At baseline HAMD-17 mean score was 8.21(4.34) and social and occupational functioning score was 71.6(14.5). Functioning and depression severity were highly inversely correlated (Pearson $r = -0.62$ at baseline and at 3 months; $r = -0.64$ at 6 months). A HAMD-17 cutoff of 5 or less had the optimal combination of sensitivity (74.5%) and specificity (74.3%). A significantly higher percentage of patients scoring 0–5 on the HAMD-17 exhibited normal functioning compared with patients scoring 6–7 (85.2% vs. 53.3%; $p = 0.006$) and a significantly higher percentage of patients scoring 6–7 on the HAMD-17 exhibited normal functioning compared with patients scoring >7 (53.3% vs. 25.9%; $p = 0.003$). Predictive factors for achieving normal functioning were: having a HAMD-17 score of 5 or less vs. >7 (Odds Ratio: 5.83) and 6–7 vs. >7 (Odds Ratio: 6.69); and exhibiting an improvement in HAMD-17 score (Odds Ratio = 1.33).

Conclusions: A score of 5 or less on HAMD-17 improved the level of agreement between normal functioning and improvement in depressive symptoms, and it is a better indicator of normal functioning compared with a score of 6–7. Our results support a lower cutoff on the HAMD-17

than the commonly used 7 o to define remission according to normal social and occupational functioning status.

P 20. Escitalopram in the treatment of Premenstrual Dysphoric Disorder (PMDD)

E. Eriksson¹, A. Ekman¹, S. Sonclair², K. Sörvik³, C. Ysander⁴, U.B. Mattson⁴, H. Nissbrandt¹

¹Department of Pharmacology, University of Göteborg, ²Läkarhuset, ³Kungälv Hospital, University of Göteborg, ⁴Institute of Clinical Neuroscience, University of Göteborg, Göteborg, Sweden

Purpose: PMDD is a chronic disease occurring in 3–8% of menstruating women. The current study was designed to evaluate the efficacy and tolerability of intermittent dosing (luteal phase only) with 10 and 20mg escitalopram.

Methods: A total of 158 patients with a diagnosis of PMDD, confirmed during two cycles of prospective self-rating of their symptoms (baseline), were treated for 3 cycles in this single-centre, randomised, double-blind, placebo-controlled 3-arm fixed dose study. The primary measure of efficacy was the relative median change from baseline in the mean of the luteal VAS rating (0–100 mm) for irritability, tension, affective lability, and depressed mood.

Results: The patients had a baseline severity of approximately 50 mm in the mean luteal VAS key psychological symptom score. At endpoint, both escitalopram treatment groups showed superior improvements on the relative median change in the key psychological symptom score versus the placebo group [86% decrease for the 10 mg escitalopram group ($p < 0.01$) and 94% decrease for the 20mg escitalopram group ($p < 0.001$) versus 69% decrease for the placebo group], with escitalopram 20mg being more efficacious than 10mg ($p < 0.01$). Escitalopram reached its maximal effect in the first treatment cycle, and this effect was maintained during the following treatment cycles. The reduction of the key symptom of PMDD, irritability, was 86% (escitalopram 10mg, $p < 0.01$), 92% (escitalopram 20mg, $p < 0.001$), and 56% (placebo). The percentage of subjects achieving remission (at least 80% reduction in the irritability score) was 30% (placebo), 60% (escitalopram 10mg) and 80% (escitalopram 20mg). The most frequent adverse event was nausea. Adaptation of patients to nausea from one treatment cycle to another was marked. The withdrawal rates due to adverse events were 6% (placebo), 13% (escitalopram 10mg) and 6% (escitalopram 20mg).

Conclusions: Intermittent treatment with escitalopram 10 and 20mg/day was effective and well tolerated in the treatment of PMDD.

Disclosures: E. Eriksson has received consultancy honoraria from H. Lundbeck A/S.

P 21. Efficacy and tolerability of Escitalopram in patients with mild, moderate and severe depression

S. Stamouli¹, A. Yfantis², A. Zouganelli³, E. Lam-pousis⁴, D. Giailoglou⁵, I. Parashos⁵

¹Psychiatric Clinic, Eginition University Hospital, Athens, ²Center for Mental Health, General Hospital, Kalamata, ³Psychiatric Clinic, Agia Barbara General Hospital, Athens, ⁴Psychiatric Clinic, Naval and Veterans Hospital, Athens, ⁵Lundbeck Hellas SA, Athens, Greece

Purpose: The effect of escitalopram increases with increasing baseline severity of the patient's depression [1]. In the present study, we examine the performance of escitalopram in patients with clinical diagnosis of depression and varying degrees of severity.

Methods: This was an open label 3-month surveillance study, conducted in 103 specialist investigational sites. Efficacy assessment was based on the CGI-S scale. Tolerability was evaluated by spontaneously reported adverse events and the treatment discontinuation rates. Statistical analysis was based on a modified intent-to-treat dataset (ITT-at least one valid post-baseline CGI-S measurement) and observed cases (OC-CGI-S measurements at all 3 visits).

Results: A total of 5175 patients were enrolled in the study, 595 (11.5%) were diagnosed as clinically suffering from mild disease (CGI-S = 2 or 3), 2261 (43.7%) from moderate (CGI-S = 4) and 2318 (44.8%) from severe (CGI-S = 5). Age and gender distribution were similar in the three severity categories. Patients with more severe illness displayed statistically significantly greater changes from baseline (multiple linear regression $p < 0.001$), in both LOCF and OC analysis. The change from baseline to the 3-month time point in the CGI-S score was –1.05 for the mildly ill, –1.89 for the moderately ill and –2.55 for the severely ill (ITT). No statistically significant differences were observed between the mildly, moderately, and severely ill patients with regard to both the total discontinuation rate (9.1% vs. 9.6% vs. 10.9%, respectively) and the frequency of adverse events (15.3% vs. 13.3% vs. 14.3%).

Conclusion: Escitalopram has greater effect in more severely ill patients and is equally well tolerated by all patients independently of the severity of the illness.

Reference

- [1] Kennedy SH, Andersen HF, Lam RW. Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. *J Psychiatry Neurosci* 2006;31:122–131.

P 22. Effects of Escitalopram on disability caused by depression

Yfantis¹, S. Stamouli², M Tzanakaki³, V. Lagari⁴, D. Giailoglou⁵, I. Parashos⁵

¹Center for Mental Health, General Hospital, Kalamata, ²Psychiatric Clinic, Eginition University Hospital, Athens, ³Psychiatric Clinic, General Hospital, Chania, ⁴Psychiatric Hospital, Tripolis, ⁵Lundbeck Hellas SA, Athens, Greece

Purpose: Escitalopram alleviates the disability caused by anxiety disorders [1]. The present study examines the effect of escitalopram in the disability of patients with clinical depression.

Methods: This was an open-label, 3-month surveillance study, conducted in 103 specialist sites. Disability was assessed using the Sheehan Disability Scale (SDS) and on 'lost days' and 'non-productive days' during the previous month. Statistical analysis was made on a modified intent-to-treat dataset (ITT: at least valid one post-baseline SDS measurement) and observed cases (OC: SDS measurements at all 3 visits).

Results: A total of 5175 patients were enrolled in the study and 1844 had disability evaluations (doctors' standard practice). These patients were younger and were more likely to suffer from comorbid anxiety and depression ($p < 0.001$). At baseline 38%, 41%, and 37% of patients reported severe or very severe disability (SDS subscale score ≥ 3) for work, social life, and family life, respectively, with corresponding mean scores $5.7 (\pm 1.8)$, $5.9 (\pm 1.8)$, and $5.6 (\pm 1.9)$. Patients' functioning improved on all SDS subscales (Hotellings' test, $p < 0.001$, LOCF and OC). At the end of the study, 80.6%, 79.5% and 83.5% of patients reported no or mild disability (SDS subscale score ≤ 2) for work, social life and family life with mean scores $2.1 (\pm 1.8)$, $2.1 (\pm 1.8)$, and $1.9 (\pm 1.7)$ (LOCF). 'Lost days' and 'non-productive days' per patient decreased from 7 and 13.4 at baseline to 1.4 and 3.3 after 3 months of treatment (LOCF). Similar results were seen for the OC dataset.

Conclusion: Escitalopram treatment produces significant improvements in the functional ability of patients with clinical depression, as measured by the Sheehan Disability Scale and by the number of 'lost' and 'non-productive days'.

Reference

- [1] Montgomery SA, Nil R, Durr-Pal N, Loft H, Boulenger JP. A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. *J Clin Psychiatry* 2005;66:1270–1278.

P 23. Unique mechanism of action of quetiapine in bipolar depression

J. Goldstein¹, G. Christoph¹, M. Brecher¹, R. McIntyre²

¹AstraZeneca Pharmaceuticals LP Wilmington USA, ²Mood Disorders Psychopharmacology Unit, University of Toronto Toronto Canada

Background: In addition to its well-characterized antipsychotic properties, quetiapine demonstrates significant antidepressant and mood-stabilizing effects in clinical trials. The pharmacology of N-desalkyl quetiapine (norquetiapine), a major metabolite of quetiapine, offers a plausible novel mechanism of action for these benefits when combined with the known properties of the parent molecule.

Methods: In-vitro pharmacological investigation of noradrenergic, serotonergic, and dopaminergic receptor and transporter targets for quetiapine and norquetiapine performed on rat and human tissues using validated assay techniques.

Results: Quetiapine and norquetiapine showed similar binding affinities for many binding targets but also substantial differences for several targets. Relevant to the antidepressant effects of quetiapine were previously unknown actions of norquetiapine on the norepinephrine transporter (NET), for which norquetiapine had high affinity (inhibition constant $[K_i] = 34.8$ nM) and was a potent inhibitor ($IC_{50} = 13$ nM); quetiapine, in contrast, demonstrated a lack of affinity ($K_i > 10000$ nM). Additionally, norquetiapine showed high antagonist affinity for serotonin 5HT_{2A} and 5HT_{2C} receptors (K_i 's = 2.93 and 18.5 nM, respectively), whereas quetiapine had lower affinity ($IC_{50} = 148$ and $K_i = 1041$ nM, respectively). Norquetiapine also had partial agonist activity at the 5HT_{1A} receptor ($K_i = 190$ nM), and quetiapine somewhat weaker affinity ($IC_{50} = 717$ nM). Quetiapine, like other atypical antipsychotics, blocked dopamine D₂ receptors, but its binding kinetics suggested minimal motor and hormonal side effects.

Conclusions: High affinity and inhibitory actions on the NET are a characteristic of drugs used to treat unimodal depression and are a major feature differentiating quetiapine from other atypical antipsychotics. Potent antagonist activity on 5HT_{2A} receptors resulting in their down-regulation is another property shared by quetiapine and SSRIs. Quetiapine has the additional effect of dopamine D₂ antagonism, which may act to stabilize mood. The unique clinical profile of quetiapine may therefore potentially be explained by its multiple effects on central monoaminergic systems mediated by the parent molecule and its major active metabolite, norquetiapine.

Supported by funding from AstraZeneca Pharmaceuticals LP.

P 24. PET-measured D2, 5HT2A, and NET occupancy by quetiapine and n-desalkyl-quetiapine (norquetiapine) in non-human primates

J. Goldstein¹, S. Nyberg², A. Takano³, S. Grimm¹, B. Gulyas³, D. McCarthy¹, C. Lee¹, C. Halldin³, L. Farde^{2,3}

¹AstraZeneca Pharmaceuticals LP, Wilmington, USA, ²AstraZeneca Pharmaceuticals, Södertälje, Sweden, ³Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Background: Clinical studies have demonstrated that quetiapine is efficacious in schizophrenia, bipolar mania and bipolar depression, with indices for efficacy also in unipolar depression, bipolar maintenance, and anxiety. Preclinical research shows that quetiapine and its major active human metabolite, norquetiapine, have moderate to high affinity in vitro for several central neuroreceptors, including D2 dopamine and 5HT2A receptors, as well as the norepinephrine transporter (NET). The present positron emission tomography (PET) study in non-human primates measured occupancy at these drug targets after single-dose administration of quetiapine and norquetiapine.

Methods: PET measurements were performed in cynomolgus monkeys. Radioligands used to determine occupancy were [¹¹C]raclopride for the D2 receptor, [¹¹C]MDL100.907 for the 5HT2A receptor, and the recently developed (S,S)[¹⁸F] FMeNER-D2 for the NET. The compounds were administered intravenously 30 min before administration of radioligand. Doses (0.15–9 mg/kg) were chosen to produce clinically relevant plasma exposures of quetiapine or norquetiapine.

Results: Plasma concentrations of quetiapine and norquetiapine were within the ranges seen during treatment with clinically recommended doses of quetiapine. After administration of quetiapine or norquetiapine, there was a dose-dependent occupancy at both D2 and 5HT2A receptors. Occupancy at D2 and 5HT2A was high for both compounds. Norquetiapine, but not quetiapine, induced high occupancy (>80%) at NET, even at low plasma concentrations ($K_i < 1$ nmol/L).

Conclusions: The observation that both quetiapine and its major human metabolite, norquetiapine, occupy D2 and 5HT2A receptors at clinically relevant plasma exposures is consistent with previous PET studies of quetiapine in patients. Using a recently developed radioligand, we found high NET occupancy by norquetiapine at clinically relevant plasma exposures. Inhibition of NET is generally accepted as a mechanism of antidepressant

activity. A combination of D2 occupancy and high occupancy at the 5HT2A receptor and NET may provide a mechanistic explanation for the broad spectrum of efficacy demonstrated for quetiapine in the treatment of psychiatric disorders.

Supported by funding from AstraZeneca Pharmaceuticals LP.

P 25. Natural killer cell in patients with major depressive disorder

S. Han, Y.W. Jeon, E.J. Park

Department of Psychiatry, Our Lady of Mercy Hospital, the Catholic University of Korea, the Catholic University of Korea, Incheon, South Korea

Objectives: In depressive illness, a wide variety of disturbances in immunologic parameters have been reported. In this study, to investigate immune system in patients with unmedicated major depressive disorder (MDD) in acute state, we measured peripheral lymphocyte subsets and natural killer cell activity (NKCA).

Methods: 41 patients met DSM-IV criteria for MDD (male 7, female 34, mean age = 53.6 ± 15.1 years) and 14 hospital staffs (male 5, female 9, mean age = 32.4 ± 3.8 years) were recruited. Peripheral lymphocyte subsets (CD3, CD4, CD8, CD19 and CD56) were assessed by flow cytometry and NKCA was measured using a standard chromium-releases cytotoxicity assay.

Results: NKCA was decreased in patients with MDD compared with normal controls (Effector:target ratio = 80:1, $F = 4.1$, $p = 0.047$) when covariates by age. But there were no differences in other peripheral lymphocyte measures including CD56 (NK T) cells.

Conclusion: NKCA was decreased in patients with MDD without a significant change in NK cell number in patients with unmedicated MDD in acute state. In this study, a change of NKCA in patients with MDD might provide the evidence for specific immune changes in patients with MDD.

P 26. Recent 5-year trends of prescription patterns in inpatients with bipolar disorder in Korea

D. Jon¹, E. Kim², H.S. Cho², E. Lee³, S. Kim², J.H. Seok¹, T.S. Kim²

¹Hallym University Sacred Heart Hospital Anyang,

²Yonsei University College of Medicine, Seoul,

³National Health Insurance Corporation Ilsan Hospital, Koyang, South Korea

Background/aims: Recent studies have suggested that newer mood stabilizers (MSs) and atypical antipsychotics (APs) have favorable efficacy and tolerability and that the combination therapy is more effective than monotherapy. The aim of this study was to

investigate the changes in prescription patterns over the course of the last 5 years.

Methods: Data of 601 patients admitted between January 2001 and December 2005 with a diagnosis of bipolar disorder was collected retrospectively from four training hospitals. Demographic variables, clinical characteristics and discharge medications over the 5-year period were analyzed.

Results: The use of valproate has increased and this trend became evident from 2004, whereas the prescription of lithium has decreased. The combination of valproate and lithium remained constant at 12% over study period. Most of the patients were on more than two psychotropic agents, the most common medication being a combination of an MS and an AP (79%). The use of typical APs has decreased obviously from 19.5% in 2001 to 7.7% in 2005. On the other hand, the use of atypical APs has increased from 71.4% to 92.3%. The most frequently used APs over 5 years were risperidone (38.5%), olanzapine (30.8%) and quetiapine (17.8%), with quetiapine showing prominent preference since 2001 and ranking as the most frequently used AP in 2005. The mean daily dosages on discharge were 1036 ± 316 mg for lithium, 934 ± 351 mg for divalproex, 13.2 ± 5.6 mg for olanzapine, 3.3 ± 1.7 mg for risperidone, and 342 ± 231 mg for quetiapine.

Conclusions: This study showed recent changes in the prescription patterns and the preference for combination therapy in bipolar disorder in Korea. The preference of two MSs combination or newer MSs was much lesser, compared to the US and European countries. These results showed relatively good adherence to recent treatment guidelines.

P 27. Psychopathology in the offspring of mothers with risk of bipolar disorder in community sample

D. Jon, H. Hong, J. Seok, N. Hong, Y. So
Hallym University, Sacred Heart Hospital, Anyang, South Korea

Background: The purpose of this study is to identify the mothers with high bipolarity of 1st grade students in elementary school and to investigate psychopathologies in the offspring of mothers with bipolarity in community sample.

Methods: This study is a part of school mental health project of Gunpo city in Korea. Subjects were 712 mothers of 1st grade students of 5 elementary schools in Gunpo city. Screening tool for bipolar disorder was Korean version of Mood Disorder Questionnaire (K-MDQ) and instruments of measurements for psychopathologies in the offspring were Behavior Assessment System for Children-2 (BASC-2) and Korean ADHD rating scale. Criteria of high bipolarity were above 7 in scores of K-MDQ and criteria of high ADHD risk in offspring

were above 80% in score of Korean ADHD rating score. The correlations among the scores of K-MDQ, Korean ADHD rating scales and subscales of BASC-2 were calculated.

Results: One hundred seventeen mothers (16.4%) were identified as risk group of bipolar disorder. There were no differences in age and education between mothers with bipolarity and without bipolarity. The offspring of mothers with high bipolarity showed higher scores of hyperactivity, aggression, conduct problems, anxiety, depression, somatization, atypicality and withdrawal in clinical scales of BASC-2. The risk of ADHD was higher in the offspring of mothers with high bipolarity. Significant correlation between manic symptoms of mother and symptoms of ADHD, hyperactivity, aggression, conduct problems, anxiety, depression, somatization, atypicality and withdrawal of their offspring.

Conclusion: These findings support the hypothesis that the offspring of mother with high bipolarity are at increased risk for developing a wide range of psychopathologies including ADHD.

P 28. Epidemiology of major depressive disorder in Korea

H. Jung¹, J-Y Lee¹, S. Kim², M. Cho¹

¹Department of Psychiatry, Seoul National University College of Medicine, ²Department of Psychiatry, Korea University, College of Medicine, Seoul, South Korea

Background/aims: Although the prevalence rate of major depressive disorder (MDD) in Asia is suspected to be lower compared to western countries, little is known about the relationship between ethnicity and MDD. This study was intended to examine the prevalence and correlates of MDD, its comorbidity with other mental and substance disorders among Korean adults via a structured clinical interview.

Methods: Data were derived from 6,275 household residents over 18 to 64 years of age who responded to Korean Epidemiologic Catchment Area (KECA) survey in 2001. Prevalence, correlates, comorbidity, and symptom profiles were estimated using Korean-Composite International Diagnostic Interview version 2.1 (K-CIDI).

Results: The overall weighted prevalence of major depressive disorder was 4.3%, 1.6%, and 1.1% (lifetime/12 months/1 month, respectively). The significant correlates of major depressive disorder were female, being unemployed, 50–59 years of age, disrupted marriage, rural habitats, and recent cohorts. Most cases of lifetime MDD (70.0%) had comorbid CIDI/DSM-IV disorders. They were anxiety disorder (46.5%), alcohol use disorder (26.3%), and tobacco use disorder (18.4%). Fatigue, insomnia, and concentration difficulties are

common symptoms (>80%) of MDD in Korean sample.

Conclusions: The prevalence of MDD in Korean sample was lower than western countries. However, the correlates, comorbidity, and common symptoms of MDD were not different from the results of western countries.

P 29. Influence social factors on level of anxiety

T. Kadyrova, N. Myrzamatova, Kyrgyz State Medical Academy, Republic Centre of Mental Health, Bishkek, Kyrgyzstan

Aim: Study level of parents' anxiety in depending of social status of family with the account ethnic features.

Methods: Psychological test "Integrative test of anxiety" (Bizyuk, 2001) developed in Russia was used.

Results: During research in prestige school of Bishkek (Kyrgyzstan) two groups of the parents aged of 35–50 years were surveyed. The first group ($n=30$) consisted parents of ethnic Kyrgyz nationality (AP- Asian Parents), second group ($n=30$) parents of Slavic origin (EP – European Parents). In the group AP the high level of anxiety (7.4 ± 0.5 , $N=4.5 \pm 0.4$) was found out ($p \leq 0.05$), and the result on a scale "anxious estimation of future" in the given group has made 53.3% ($p \leq 0.05$). In the group EP the almost normal level of anxiety (4.6 ± 0.4) was revealed, "anxious estimation of future" has made only 10.0%. The comparison of the social status of two groups has shown that in group AP the parents occupy the high social status in official state institutions and in the greater degree were concerned with instability in the country, as could be dismissed (AP 49 ± 1.2 , EP 7 ± 0.6 $p \leq 0.05$). In the group EP the parents were engaged in private business, did not have fear to lose job and were sure in the future.

Conclusion: The revealing of high level of anxiety in respondents should be considered as factor for realization of medical measures, in particular of family therapy. Also it is important information at consultation not only adults but also children. High level of anxiety at parents, as a rule, promotes the appearance the emotional and behavioral disorders at children.

P 30. Different pattern of surface shape deformity of thalamus between obsessive-compulsive disorder and schizophrenia

D. Kang¹, S. Kim², C. Kim¹, J. Choi¹, J. Jang¹, M. Jung¹, J. Lee², J. Kwon¹

¹Department of Psychiatry, Seoul National University College of Medicine, Seoul, ²Department of Biomedical Engineering, Hanyang University, Seoul, South Korea

Obsessive-compulsive disorder (OCD) and schizophrenia have not only been suggested to share clinical symptoms in some patients but also to share dysfunctional frontal-subcortical circuitry. This study was designed to clarify different patterns of abnormalities of specific thalamic nuclei between OCD and schizophrenia compared with healthy comparison groups, although thalamic abnormality is implicated to the two illnesses in common at a gross anatomical level. We performed 3 dimensional shape deformation analyses of the thalamus in three age- and sex-matched groups of 22 patients with OCD, 22 patients with schizophrenia and 22 normal subjects. The most prominent surface deformities in OCD were outward deformities in the anterior, lateral portion of the thalamus (right > left) and in the posterior portion of the left thalamus. On the contrary, the most prominent surface deformities in schizophrenia were outward deformity in the dorsomedial portion of the left the thalamus and in the posterolateral portion of the right thalamus. In terms of the thalamic asymmetry, both OCD and schizophrenia patients revealed loss of a leftward pattern of asymmetry on the posterior, medial surface of the thalamus and exaggeration of rightward pattern of asymmetry on the posterior, lateral surface of the thalamus. Our findings suggest that different patterns of abnormalities of specific thalamic nuclei may be related with the different phenomenology of OCD and schizophrenia.

P 31. The use of quetiapine as an adjunct in the pharmacotherapy of generalised anxiety disorder: a flexible-dose, open-label trial

M. Katzman^{1,2,3}, M. Vermani¹, L. Jacobs¹, M. Marcus¹, B. Kong B¹, S. Lessard⁴, W. Galarraga⁵, L. Struzik¹, C. Iorio¹, A. Gendron⁶

¹START Clinic for Mood and Anxiety Disorders, ²University of Toronto, ³Northern Ontario School of Medicine, ⁴University of Ottawa, ⁵Mont Fort Hospital, ⁶Behavioural Science Program McMaster University, ⁶Astrazeneca Canada inc., Mississauga, Ontario, Canada

Background: Generalised anxiety disorder (GAD) is a chronic disorder associated with significant morbidity and disability. Traditional therapies are associated with poor levels of remission, and often result in troublesome side effects.

Methods: This was a 12-week, open-label, flexible-dose study to assess the efficacy and tolerability of quetiapine as an adjunctive treatment to traditional medication. A total of 40 outpatients with GAD who had not achieved remission following at least 8 weeks of an adequate dose of traditional therapy were enrolled. The primary endpoint was the mean change from pre-treatment to Week 12 in Hamilton Anxiety Rating Scale (HAM-A) total scores. Secondary end-

points included: the proportion of patients achieving remission (HAM-A total score ≤ 10 at Week 12), Clinical Global Impressions-Severity of Illness (CGI-S), Clinical Global Impressions-Global Improvement (CGI-I), Pittsburgh Sleep Quality Index (PSQI) and Penn State Worry Questionnaire (PSWQ).

Results: Adjunctive quetiapine significantly reduced HAM-A total scores from pre-treatment (29.8 ± 9.0) to Week 12 (9.0 ± 10.2) (-20.6 ; $p < 0.001$). The HAM-A remission rate was 72.1% at Week 12. Augmentation of traditional therapies with quetiapine resulted in a significant reduction in all efficacy measures by study end. Quetiapine was well tolerated: the most common adverse event (AE) was sedation, with no incidence of serious AEs and no clinically significant changes in vital signs or laboratory assessments.

P 32. Quality of Web based information on social phobia

Y. Khazaal, A. Chatton, S. Cochand, D. Knobel, D. Zullino

Division of substance abuse, Geneva University Hospitals, Geneva, Switzerland

Objective: To evaluate the quality of web-based information on social phobia and to investigate particular quality indicators.

Methods: Two keywords, Social phobia and Social Anxiety Disorder, were entered into five popular world wide web search engines. Websites were assessed with a standardized proforma designed to rate sites on the basis of accountability, presentation, interactivity, readability and content quality. "Health On the Net" (HON) quality label, and DISCERN scale scores aiding people without content expertise to assess quality of written health publication, were used to verify their efficiency as quality indicators.

Results: About 200 identified links, 58 pertinent websites were evaluated. Based on outcome measures used, overall quality of sites turned out poor. DISCERN and HON label are good quality indicators.

Conclusions: While patient social phobia education Web sites are common, educational material is highly variable in quality and content. There is a need for better evidence based information about Social phobia on the web, and a need to reconsider the role of accountability criteria as indicators of site quality whereas HON label and DISCERN may be useful indicators.

P 33. Impact of depression on work productivity in employees who visit psychiatric clinic

W. Kim, J.M. Woo

Seoul Paik Hospital, Inje University, Seoul, South Korea

Objective: Depressive disorder causes patients' distress and makes socioeconomic burden both di-

rectly and indirectly. Absenteeism and presenteeism represents the lost productivity of employee, and the impact of depression on productivity is considered substantial. Therefore, we tried to calculate the absenteeism and presenteeism in depressive workers who visit psychiatric clinic and figure out the difference between depressive workers and controls.

Methods: Patient group were recruited from workers visiting psychiatric outpatient clinic who had depressive disorders without physical illness and other mental disorders ($N=106$). Age and sex matched healthy control group were also recruited from advertisement through website ($N=100$). WHO Health and Work performance Questionnaire (HPQ) was applied to measure lost productive time and HAM-D was rated. Statistical analysis was performed with independent t-test or χ^2 test as characteristics of values ($p=0.05$).

Result: The number of absence (0.94-day/month vs. 0.10-day/month, $p=0.015$) and the number of early leaving (2.56-day/month vs. 0.24-day/month, $p<0.001$) is significantly high in the depression group. The depression group evaluated their performance level lower than normal control group with significant value (5.16 vs. 7.62, $p<0.001$). And, the depression group estimated their performance level during recent 4weeks much lower than during past 1-year (5.16 vs 6.63, $p<0.001$). The estimated cost of absenteeism in depression group is higher than controls by 2,640 US dollars/year/person, and those of presenteeism in depression group is also higher by 5,140 US dollars/year/person. Therefore, the total cost of LPT in depression group is higher than controls by 7,780 US dollars/year/person. This may be estimated as 26% of mean annual salary in the depression group.

Conclusion: Depression contributed to lost productive time among workers substantially in our study and this implies that depressive disorders in employees make a bad impact on organizational productivity and international competitiveness. It is also important that the presenteeism was prominent than the absenteeism in the aspect of management. For improving the productivity in work place, the monitoring and proper management of mental health is considered essential.

P 34. Association study of A2a Adenosine receptor gene polymorphism

W. Kim, J.M. Woo

Seoul Paik Hospital, Inje University, Seoul, South Korea

Objective: The adenosine A2a receptor (A2aAR) is thought to be implicated in the pathogenesis of panic disorder because caffeine, a potent antagonist for A2aAR, can precipitate panic attacks, and because

disruption of the A2aAR gene increases anxiety-behaviors in mice. Recent studies demonstrated that the A2aAR 1976CT genetic polymorphism confers susceptibility to panic disorder in Caucasian, though not in Asian. The present study tested the hypothesis that the A2aAR 1976CT genetic variant confers susceptibility to panic disorder in Korean.

Methods: 258 patients with panic disorder and 117 healthy controls participated in this study. Genotyping was performed by polymerase chain reaction-based method.

Results: Genotype ($P=0.389$) and allele ($P=0.655$) distribution of adenosine A2a receptor (A2aAR) polymorphism patients with panic disorder was not significantly different from those of the controls. However, panic disorder with major depressive disorder showed significant association with 1976C allele ($P=0.008$) and A2aAR 1976CT genotype ($P=0.008$).

Conclusion: This study suggested that the adenosine 1976CT polymorphism may have a potential role for susceptibility to panic disorder with major depressive disorder in the Korean population. This calls for consecutive studies in order to understand the association of A2aAR polymorphism and various psychiatric disorders.

Keywords: panic disorder, adenosine, polymorphism, Korean

P 35. Association between serotonin-related gene polymorphisms and panic disorder

Y. Kim¹, H.K. Yoon¹, J.C. Yang², H.J. Lee¹

¹Departement of Psychiatry, Korea University, College of Medicine, Seoul, ²Departement of Psychiatry, Chunbuk National University, Chunju, South Korea

We investigated the 5-HT_{2A} receptor (5HTR_{2A}) and tryptophan hydroxylase (TPH) genes for association with panic disorder (PD). All of the PD patients were given a diagnostic assessment based on clinical interviews using the Structured Clinical Interview for DSM-IV (SCID). The severity of their symptoms was measured using the Spielberger State-Trait Anxiety Inventory (STAI), Panic disorder severity scale (PDSS), Anxiety Sensitivity Index (ASI), Acute Panic Inventory (API), Beck Depression Inventory (BDI), Hamilton's rating scale for Anxiety (HAMA), and Hamilton's rating scale for Depression (HAMD). However, we found a significant difference in symptom severity among the genotypes of both the 5HTR_{2A} 1438A/G and 102T/C polymorphisms. Although there were no significant differences in the genotype and allele distributions, we found a significant association between panic symptom severity and the serotonin 2A receptor gene. This result suggests that the serotonin 2A receptor and serotonin may play a

significant role in the pathogenesis of panic disorder. This is the first study to suggest a possible relationship between serotonin 2A receptor gene and panic symptom severity. More work is needed to further replicate these findings and further investigate PD candidate genes associated with the serotonin system.

P 36. Temperament and character in subjects with obsessive-compulsive disorder

S. Kim, C-H. Kim

Department of Psychiatry and Institute of Behavioral Science in Medicine, Yonsei University Seoul South Korea

Background: The objective in this study was to evaluate the differences of personality traits between OCD patients and normal populations using the Temperament and Character Inventory (TCI) and also to examine the relationship between personality traits and the severity of OC symptoms in OCD patients. Additionally, we wanted to assess the influence of particular personality traits on dimensional phenotypes of OCD.

Methods: We recruited 130 OCD patients and 185 normal controls. All subjects completed the TCI. We also assessed the OCD patients with Y-BOCS, Hamilton Depression Rating Scale and with factor-analyzed symptom dimension scores using Y-BOCS checklist.

Results: There were significant differences in the TCI subscales between OCD patients and control subjects (MANOVA, Hotelling's Trace $F=25.94$, $p<0.001$). OCD subjects were characterized by higher Harm Avoidance (HA) ($F=127.4$, $p<0.001$) scores and lower Reward Dependence (RD) ($F=12.7$, $p<0.001$), Cooperativeness (C) ($F=91.3$, $p<0.001$) and Self Directedness (SD) ($F=53.9$, $p<0.001$) scores than controls. The TCI subscales of both OCD and control subjects are follows. OCD – HA 25.1 ± 5.6 , NS 17.9 ± 4.1 , RD 14.1 ± 2.9 , P 4.1 ± 1.6 , SD 20.1 ± 7.1 , C 24.0 ± 7.2 , and Self Transcendent (ST) 10.0 ± 4.3 , and control-HA 16.5 ± 7.4 , Novelty Seeking (NS) 18.2 ± 5.9 , RD 15.5 ± 3.8 , P 4.1 ± 1.8 , SD 26.4 ± 7.6 , C 31.0 ± 5.8 , and ST 10.8 ± 5.6 . In multiple regression, higher HDRS ($\hat{a}=0.23$, $p=0.006$) and lower SD ($\hat{a}=-0.40$, $p<0.001$) and C ($\hat{a}=0.37$, $p<0.001$) scores significantly predicted higher Y-BOCS scores. In multiple regressions of factor-analyzed symptom dimensions, the SD was a predictor of higher scores on all OC symptom dimensions: symmetry/ordering ($\hat{a}=-0.29$, $p=0.001$), hoarding ($\hat{a}=-0.36$, $p<0.001$), contamination/cleaning ($\hat{a}=-0.28$, $p=0.001$), aggressive/checking ($=-0.38$, $p<0.001$), and sexual/religious obsessions ($\hat{a}=-0.38$, $p<0.001$) dimensions.

Conclusions: In summary, our study showed that OCD subjects have higher HA scores and lower SD,

RD and C scores than controls. The lower SD and C scores are associated with the severity of OC symptoms measured by the Y-BOCS. Lower SD scores also predict higher factor-analyzed symptom dimension scores from the Y-BOCS checklist.

Keywords:

P 37. Gender dimorphic association between obsessive-compulsive disorder and 5-HT1DB, DRD4, and MAOA gene

C. Kim¹, S-J. Kim

Department of Psychiatry and Institute of Behavioral Science in Medicine, Seoul, South Korea

Background: The serotonergic and dopaminergic dysregulation are most popular hypotheses for OCD. The 5-HT1Db receptor is a terminal autoreceptor involved in the regulation of 5-HT neurotransmission. Meanwhile, because of the phenomena of emerging OC symptoms after treatment with clozapine, the dopamine receptor D4 (DRD4) gene has been the focus of genetic studies of OCD. Also, monoamine oxidase A (MAOA) gene has received attention because MAOA involves in metabolism of serotonin and dopamine. However, there have been significant inconsistencies in the results of relationship between these genes and OCD. One of major causes of these inconsistent findings is gender dimorphism of OCD in genetic study. Therefore, we have investigated the associations between 5-HT1Db, DRD4, and MAOA gene and OCD in both male and female separately.

Methods: 120 male OCD patients and 101 normal male controls were participated in this study. Genomic DNA was extracted from venous blood.

Results: The genotype frequencies of G861C polymorphism of 5-HT1Db in OCD and control groups were followings; In males, there were significant differences of genotype frequencies of HT1Db between OCD and control groups. ($\chi^2 = 11.36$, $p = 0.003$). In females, there were no significant differences of genotype frequencies of HT1Db between OCD and control groups. ($\chi^2 = 4.3$, $p = 0.1$). The genotype frequencies of 48 bp VNTR polymorphism of DRD4 in OCD and control groups were followings; In males, there were significant differences of genotype frequencies of DRD4 between OCD and control groups. ($\chi^2 = 15.4$, $p < 0.001$). In females, there were no significant differences of genotype frequencies of DRD4 between OCD and control groups. ($\chi^2 = 0.0$, $p = 1.0$). In males, there were significant differences of allele frequencies of MAOA VNTR between OCD and control groups. ($\chi^2 = 8.3$, $p = 0.004$). In females, there were significant differences of genotype frequencies of MAOA VNTR between OCD and control groups. ($\chi^2 = 4.5$, $p = 0.10$). *Conclusions:* We could find associations between OCD and G861C polymorph-

ism of 5-HT1Db, 48 bp VNTR, and MAOA VNTR of DRD4 only in males.

Keywords:

P 38. Life Quality of Depressed, Somatically Ill and Average Child Populations

E. Kiss, D. Skultéti, A. Vetró

Child Psychiatry Unit, University of Szeged, Hungary

Background and aim: Illnesses negatively influence subjective quality of life in children. Many studies examine the effect of somatic illnesses on QoL, less the influence of psychiatric disorders and very few comparing the effect of different types of diseases to each other and to a control population in children. Our hypotheses were the following: Chronic respiratory illness (CRI) and Major Depressive Disorder (MDD) negatively affect the quality of life (QoL); parents of ill children rate the quality of life of their children lower than children themselves; most problematic area of the quality of life for children with MDD is mental health, for children suffering from CRI is physical health and for the average population is school.

Methods: The depressed sample consisted of children with DSM IV Major Depressive Disorder ($N = 100$). The mean age of the sample was 11.22 years (sd: 2.84 years, range: 7 to 18 years). There were 55 boys and 45 girls. The somatically ill sample contained children with chronic respiratory illness ($N = 74$). There were 41 boys (55.4%) and 33 girls. The mean age of this sample was 10.99 years (sd: 3.46 years), the age range was 6 to 19 years. Asthma bronchiale was diagnosed in 73% of the sample. The control population consisted of 300 children tested in elementary schools. Children were aged 6 to 16 years (mean: 10.76 years, sd: 2.92 years). There were 164 boys (54.7%) and 136 girls.

Measures: The Inventory of Life Quality in Children and Adolescents (ILK) was used to measure subjective quality of life. Children completed the questionnaire about themselves, parents about their children. The sum of the individual items was calculated to obtain an overall satisfaction.

Results: Children in the school-based population were most satisfied, depressed children were least satisfied. Parents of depressed children rated quality of life of their offsprings lower than children themselves. Parents in the respiratory problem group did not show significant difference with their kids, while parents in the control group rated better quality of life for their kids, than the children. Most problematic areas were mental health and school for the depressed, physical and mental health for the somatically ill and alone activities and school for the school-based population.

Conclusion: Both somatic and mental illness influence quality of life of children, but depression seems to have a stronger negative effect. It is important to

get information from both children and parents due to differences in opinion.

P 39. Poly- and Multipsychopharmacy in psychiatric inpatient populations of three European countries: Data from AMSP (Arzneimittelsicherheit in der Psychiatrie), a European pharmacovigilance system

A. Konstantinidis¹, U. Moser¹, G. Pail¹, R. Grohmann², A. Horvath³, R. Engel², S. Kasper¹

¹Division of Biological Psychiatry, Medical University of Vienna, Austria, ²Department of Psychiatry, Ludwig Maximilians University, Munich, Germany,

³Psychiatric Private Clinic Sanatorium Kilchberg/Zurich, Switzerland

Introduction: Although psychotropic polypharmacy is widely used in common practice, lacks sound clinical evidence of its putative effect [1]. Psychiatric textbooks and international guidelines advise monotherapy wherever possible and report a higher risk of adverse drug reactions under polypharmacy [2].

Methods: The AMSP study [2] is a drug safety program that ensures the continuous assessment of severe adverse drug reactions (ADR) in psychiatric inpatients under the natural conditions of routine clinical treatment. Furthermore, on two reference days per hospital and per year, the following data are recorded for all patients on the wards under AMSP surveillance: all drugs applied on that day with the daily dosage for psychotropic drugs, ICD diagnosis, age, and sex. Data is stored at the study center in Munich. Due to the increasing number of participating clinics over the years only data of 33 hospitals (5 Austrian, 22 German and 6 Swiss institutions) who participated since 2003 were analyzed. In our study we defined the use of two or more psychotropics of the same class as polypharmacy and the use of two or more psychotropics from different classes as multipharmacy.

Results: Over 5000 inpatient-data were recorded per year between 2003 and 2005 (2003 $N=5993$; 2004 $N=6979$; 2005 $N=6400$). An increase in the mean number of psychotropic medication used from 2003 to 2005 was found in all three countries; Germany showing the lowest mean number of psychotropics per inpatient with 2,48 on 2003 and 2,47 on 2005, followed by Switzerland with 2,62 and 2,77 and Austria with 3,08 to 3,2. Although in all three countries the number of antidepressants or antipsychotics prescribed per inpatient remained stable or increased slightly over the years, the use of more than one class of psychotropics per inpatient could be identified as the cause for multipharmacy. All participating countries showed a high percentage of neuroleptics in depressed inpatients and of antidepressants and anticonvulsants in schizophrenic inpatients. In detail, in 2003 47,45% of the depressed

inpatients received a neuroleptic, in 2005 51,24%. 21,89% of the schizophrenic inpatients received an antidepressant and 20,18% an anticonvulsant in 2003, in 2005 the rates raised to 22,71% and 22,84%, respectively.

Conclusion: Polypharmacy and especially multipharmacy is still gaining ground despite the recommendations for monotherapy by international experts. Further studies should investigate the combinations most commonly used introducing future studies, which should evaluate a possible putative effect of psychotropic combinations.

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P 40. Mapping white matter alterations in obsessive-compulsive disorder

J. Kwon¹, D.H. Kang¹, B.M. Gu², W.H. Jung², J.Y. Park², J.S. Choi¹, M.H. Jung¹

¹Department of Psychiatry, Seoul National University College of Medicine, ²Interdisciplinary Program in Brain Science & Cognitive Science, Seoul, South Korea

Recently, considerable evidence suggests that pathological changes in patients with OCD may be expressed at the level of spatially distributed network that subsumes the multiple, densely interconnected cortical and subcortical cortex. The aim of the current study was to investigate the white matter abnormalities in patients with obsessive-compulsive disorder (OCD) compared with healthy volunteers employing diffusion tensor imaging. Twenty-six patients with OCD and 26 healthy comparison subjects matched for age, sex, and handedness underwent diffusion tensor imaging and structural magnetic resonance imaging examinations. Fractional anisotropy (FA) was compared between groups on a voxel-by-voxel basis. Compared with healthy volunteers, patients with OCD showed significant increase in FA in the parietal white matter. Our findings provide evidence of an abnormality that involves the white matter integrity of frontal-parietal networks in the pathogenesis of OCD.

P 41. Does a diagnosis of depression or the prescription of an antidepressant influence hypnotic use in primary care?

M. Lader¹, J. Donoghue²

¹Institute of Psychiatry, Kings College, London, United Kingdom, ²School of Pharmacy & Chemistry, John Moores University, Liverpool

In 1997, the commonest treatment for insomnia was a prescription for a benzodiazepine: constraints on resources meant that these drugs were likely to remain the mainstay of treatment even though the potential for the development of dependence limited the value of these medicines to the short term [1]. Despite this, a contemporary review of psychotropic medicines stated that insomnia was not a sufficient reason to prescribe a benzodiazepine [2]. The BNF stated that hypnotics should be prescribed for severe insomnia only, for a maximum of 2–4 weeks. In 2004, The National Institute for Health and Clinical Excellence recommended that an hypnotic drug could be considered appropriate in severe insomnia only, when it should be prescribed for only a short period of time [3]. However, no recommendations or surveys of hypnotic use have taken into account the need to manage disturbed sleep in depression, a key symptom experienced by between 50% and 90% of patients. This study investigated the impact of a diagnosis of depression or the prescription of an antidepressant on hypnotic treatment in patients newly prescribed an hypnotic in primary care in the UK.

Method: Data relating to new hypnotic prescriptions for 10 years (1996–2005) were obtained from the DIN-Link database which currently contains over 750,000 patients closely matching the socio-demographic profile of the UK as a whole. Patients (> 18 years) were included if they received a new prescription for an hypnotic medicine (they could not have received a prescription for any anxiolytic or hypnotic medicine in the previous 12 months) and followed up for 1 year. Data were obtained on gender, age, drug prescribed, dose, length of treatment, whether there had been a diagnosis of depression, and whether they had been prescribed an antidepressant.

Results: Throughout the study, the length of treatment with hypnotics in primary care in the UK did not conform to good practice as recommended in national guidelines, though the total number of patients newly prescribed an hypnotic fell from 6098 in 1996 to 4278 in 2005, a fall of 30%. The proportion of patients newly prescribed an hypnotic who also received a diagnosis of depression increased from 11.1% to 17.4%. For each year of the study, a diagnosis of depression was associated with an increase in the length of treatment with hypnotics: in 2005, the average length of continuous treatment with an hypnotic in depressed patients was 80 days – 30% higher than non-depressed patients. The co-prescription of an antidepressant with an hypnotic had similar results: in 2005, the proportion of depressed patients prescribed an antidepressant who received an hypnotic for more than 3 months was 31% – over 10 times greater than those not prescribed an antidepressant.

Conclusions: In patients newly prescribed an hypnotic medicine, a diagnosis of depression or the prescription of an antidepressant increases the length of hypnotic treatment, suggesting that disturbed sleep is an intractable feature of depressive illness, and that commonly prescribed antidepressants may not offer effective treatment for this aspect of the illness. More research is needed to determine the best ways of managing disturbed sleep in depression.

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P 42. Therapeutics effects of pregabalin in anxiety disorders

A. Lera

Operative Unit Psychiatry, Giulianova, Italy

We tried to take into consideration a possible positive function of the pharmacological treatment with Pregabalin, on the Anxiety reduction. Twenty subjects, aged between 25 and 40, with Anxiety Disorder, were submitted, before the call up to the study, to a Pscodiagnostic estimate evaluation through the administration of the Hamilton-A test, which showed a point between 15 and 27. Afterwards, ten subjects, was submitted to Pregabalin at 150 mg/day, for six months. A check group, instead, containing the same number of people, didn't carry any pharmacological therapy. At the end, both the study group and the check group, that is all the twenty patients, were submitted to another estimate. We have obtained a decrease of anxiety in 70% of cases. The points, obtained comparing the first Hamilton-A test with the check one, have shown a decrease of 10 points in 15%, 8 points in 35%, 7 point in 20%, with an immutable condition in 30% of cases.

Therefore the result has been achieved only for the patients submitted to pharmacological treatment with Pregabalin at 150 mg/day. They should improve life quality, reducing the frequency and the intensity of anxiety disorders.

We can say, that in the study group, submitted to pharmacological treatment with Pregabalin, life quality, valued through the Hamilton-A, is improved significantly. This is a noteworthy result for Pregabalin, in the reduction of the anxiety disorders and the alleviation of their seriousness.

P 43. Perfect NERIT (Neuromuscular Emotional Relaxing Treatment Integrated): a new therapeutic methodic in anxiety disorders

A. Lera

Operative Unit Psychiatry, Giulianova, Italy

Our hypothesis in this study is that, through the treatment with PERFECT NERIT, the related well being reduces cortisol level and both related anxiety. We examined forty female patients suffering from Anxiety Disorder, aged between 30 and 50. The half of subjects was submitted to treatment with Perfect Shape, a new motor method, taking into consideration a possible positive function on the anxiety. The remaining half acted as check group. Everybody was submitted, before the call up to the study, to a preliminary salivary cortisol level and Psycodiagnostic evaluation through the administration of the Hamilton-A test which showed a point between 15 and 27, our patients weren't also submitted to any therapy. Afterwards, the study group, including twenty subjects, was submitted to Perfect Nerit which lasted four months, with following prolongation activities for further two months. A check group, instead, containing the same number of people, didn't carry out any therapy. At the end of eight months, both the study group and the check group, that is all the patients, were submitted to another salivary cortisol level and Psycodiagnostic evaluation. We have obtained a decrease of cortisol level in 54% of cases and of anxiety in 78% of cases. The points, obtained comparing the first Hamilton-A test with the check one, have shown a decrease of 9 points in 18%, 8 points in 25%, 10 point in 35%, with an immutable condition in 22% of cases.

On the basis of the results, we can assert that in the study group, submitted to Perfect Shape, anxiety, valued directly through Hamilton-A test and indirectly through salivary cortisol level, is reduced, even though in the least way. This is a noteworthy result, above all in relation to the immutable cognitive balance of the check group. The Perfect Nerit, seem to have a positive function in the reduction of the anxiety dimension and in the improvement of life quality.

P 44. Comparison of time to rehospitalization among patients with schizophrenic disorder, bipolar disorder, or major depressive disorder

C. Lin, Y-S. Chen, M-C. Chen, L-S. Chou, K-S. Lin, C-Y. Lin

Kai Suan Psychiatric Hospital, Kaohsiung, Taiwan

Background and aims: A subpopulation of chronically mentally ill patients, sometimes referred to as revolving door patients, are frequently readmitted to psychiatric units. The purpose of this study was to compare the time to rehospitalization of patients with schizophrenic disorder, bipolar disorder, or

major depressive disorder. Other factors, which may influence time to rehospitalization, were also examined.

Methods: Rehospitalization status was monitored for all admitted inpatients with schizophrenic disorder ($n=336$), bipolar disorder ($n=117$), and major depressive disorder ($n=90$), from January 1, 2002 to December 31, 2002. Time to rehospitalization within one year after discharge was measured by the Kaplan-Meier method. Risk factors associated with rehospitalization were examined by the Cox proportional hazards regression model.

Results: The three groups were comparable for comorbid alcohol abuse/dependence, age, and years of education. No significant difference was observed among three diagnoses for the time to rehospitalization (log rank = 0.570, $df=2$, $p=0.752$). The major depressive disorder diagnosis had shorter follow-up time (log rank = 10.21, $df=2$, $p=0.006$). Number of previous admission ($B=0.087$, hazard ratio = 1.091, 95% CI = 1.062–1.121, $p=0.000$) was associated with higher risks of rehospitalization.

Conclusion: This study demonstrated that the three diagnoses had similar influences on time to rehospitalization. Further research should be carried out to test risk factors in a prospective study, and to assess the cost-effectiveness of interventions to prevent rehospitalization.

P 45. Genetic bases of comorbidity between mood disorders and migraine: possible role of Serotonin Transporter Gene

C. Lorenzi, F. Buongiorno, E. Marino, A. Pirovano, L. Franchini, E. Smeraldi

Ospedale San Raffaele, Universita' Vita-Salute, Milan, Italy

Migraine is a common neurological disorder that affect up to 15% of the general population and it is related to sex. When some neurological symptoms prelude migraine episodes, it is called "migraine with aura".

Many studies demonstrated a relationship between migraine and mood disorders. Among many possible biological causes of mood disorders, impairments in serotonergic system is one of the most validate. On the other hand, for decades, serotonin has been speculated to play a major role in migraine pathophysiology. A recent study showed a significant increase of brainstem serotonin transporter (SERT) gene availability in migraineurs, suggesting a dysregulation of serotonergic system.

So, we hypothesised that migraine and depression could be due to an impairment of a common biological pathway.

Methods: The sample consisted of 96 patients affected by mood disorders in concomitant migraine (29 with aura, 67 without it).

The sample was genotyped for SERTPR, a functional polymorphism located in the SERT promoter region. It consists of a 44-bp insertion/deletion causing the presence of long/short (l/s) alleles.

Results: In our sample, 58.3% of subject had almost a relative affected by mood diseases ($P < 0.02$) and 55.2% of subjects had familiarity for migraine ($P < 0.00001$). Moreover, we found the comorbidity between mood disorders and the existence of migraine ($P = 0.0001$).

Then, we distinguished the subjects in unipolar and bipolar and we detected the onset of mood disorder and the migraine: in both samples, we found that, onset of migraine is earlier than onset of mood disorder ($P < 0.0001$).

Genetic analysis showed a significantly ($P < 0.0001$) late onset of mood disorder, in subjects carrying SERTPR l/l genotype, independently from age of onset of migraine.

Conclusion: Our study confirmed the heritability of mood disorders and migraine, also when in comorbidity each other. Moreover, we validated the role of SERTPR in modulating onset of mood disorders, while, probably because of the paucity of our sample, we didn't elucidate a clear role of this polymorphism in migraine.

P 47. The evaluation of the vascular risk factors for Alzheimer disease in prodromal depressive syndrome associates with MCI

D. Marinescu, L. Mogoanta, T. Udristoiu
University of Medicine and Pharmacy of Craiova, Craiova, Romania

Background: The most frequent prodromal disorder in Alzheimer disease is depression, which precedes the MCI phase with approximately 5 years, and the cerebral vascular disturbances constitute an important risk factor for rapid cognitive destructure. The biochemical mechanisms implicated in the rapid cognitive decline have as a main target the hippocampus, and they are:

- The cholinergic blockage;
- Dopamine and noradrenalin deficit;
- Glucocorticoid aggression.

For depression, on animal model, is accredited both anticholinergic blockage and the model of induction with dexamethasone. The use of tricyclic antidepressants with an important anticholinergic effect may modify the evolution of the cognitive decline to the patients with depression and MCI.

Materials and method: We used four comparative lots on rats (N1 – control, N2 – dexamethasone, N3 – dexamethasone + amitriptyline, N4 – dexamethasone + trazodone). The study animals were sacrificed on the 14th day.

Results: Important changes of the cytoarchitecture at the frontal cortex, dentate gyrus and

the hippocampic zone (vacuolizations and pinocytosis) and important vascular changes (neofunctional vessels, blood extravasation) were observed in N3 lot.

The cytoarchitectural and vascular changes to the N4 lot were significantly reduced, trazodone not having an anticholinergic effect.

Conclusions: The presence of the anticholinergic mechanism to some of the antidepressive substances, seems to potentiate both the cerebral structure and the vascular factor which can be responsible for therapeutical resistance of depression and the acceleration of cognitive decline.

P 48. Role of serotonergic gene polymorphisms on response to Transcranial Magnetic Stimulation in depression

E. Marino, D. Rossini, A. Malaguti, C. Lorenzi, A. Pirovano, L. Polledri, R. Zanardi, A. Lucca, E. Smeraldi
Ospedale San Raffaele, Università Vita-Salute, Milan, Italy

Background: Transcranial magnetic stimulation (TMS) is a non-invasive method used to stimulate and modify the activity in target cortical areas of human brain. TMS has been extensively studied as an efficacious treatment for Major Depression.

However, no data are available, up to now, about the role of genetic variables on the response to this treatment.

Methods: The sample consists of 99 bipolar or unipolar patients.

It was genotyped for two polymorphisms of serotonergic system. The first is a polymorphism of the serotonin transporter promoter region (SERTPR). It consists of a 44-bp insertion/deletion causing long/short (l/s) alleles. The basal activity of the long variant is more twice than the short.

The second is a polymorphism of the serotonergic receptor promoter region (5-HT1A -1019C/G).

Patients were randomly assigned to two different groups: active or sham rTMS.

Results: There is a significant influence ($P = 0.016$) of the SERTPR polymorphism on response, but the influence is not different between active and sham stimulation. On the other hand, there is a trend toward significance for the influence of 5-HT1A polymorphism on the response of the whole sample, and a statistically significant ($P = 0.014$) interaction between 5-HT1A genotype and type of stimulation. C/C patients show a higher difference between active and sham stimulation, indicating that these patients get more benefit from TMS than C/G and G/G subjects.

Conclusion: About SERTPR, patients with s/s genotype have a worse response to SSRI than patients with the l allele. However, there is no difference

between active and sham stimulation, indicating that it don't affect the response to active TMS.

Concerning 5-HT1A, C/C patients are best responders to SSRI and, treated with active TMS, they have significantly better results than sham treated patients.

It is possible that the serotonergic neurotransmission of those patients with a lower 5-HT1A function (C/C patients), is more affected by down-regulation of such function observed after TMS treatment.

This study proves a significant relationship between 5-HT1A and TMS.

P 49. Topiromate efficacy and tolerability at adolescents with posttraumatic disorder (PTSD) which have comorbid panic disorder (PD) or depression

I. Martsenkovsky, Y. Bikshaeva, Martsenkovska
Ukrainian Research Institute of Social and Forensic Psychiatry and Drug Abuse, Kyiv, Ukraine

Background: Preliminary findings suggest that topiromate is effective in PTSD. However, as over 40% of adolescent with PTSD have comorbid PD and/or depression. Our purpose was the proof of influence topiromate on anxiety and panic semiology in comparison with placebo and SSRI.

Methods: Inclusion criteria: primary DSM-IV diagnosis of panic disorder, with or without agoraphobia, 4 or more panic attacks in the 4 weeks prior to screen evaluation; minimum score 18 on the HARM-D and/or HARM-A. Therapy was received by 86 teenagers in the age of from 14 up to 21 years. The basic group received topiromate, the group of comparison received SSRI (sertraline, citalopram). Studies utilized a flexible dosing regimen (100–150 mg/day). Key efficacy measures included the change from baseline in the CAPS-2 total score and CGI responder analyses. Presence of baseline comorbid disorder was determined using the HARM-D and HARM-A.

Results: The reduction in the CAPS-2 total score observed with topiromate was statistically significantly greater then that seen with SSRI at week 10 endpoint (treatment difference – 10.40; 95%; CL-13.4, -7.38; $P < 0.001$). A statistically significantly greater proportion of topiromate-treated patients (50%) than placebo treated patients (10%) were defined as treatment responders based on the CGI (much or very much improved) [adjusted odds ratio = 2.30; 95%; CI 1.77, -2.97; $P < 0.001$].

Conclusions: Topiromate is effective and well tolerated [in treatment of PTSD, comorbid PD and/or depressive. The proved efficiency and good bearableness topiromate are very important for practice

as opportunities of application SSRI are limited because of higher, than at adults of risk of suicide actions.

P 50. Impact of culture on male and female patients coping with pain

Mahnoor Masood, K. S. Malik, Mahrukh Masood
Shalamar Hospital, Lahore, Pakistan

Aim: To investigate effects of culture on types of coping strategies employed by male and female patients.

Method: 65 patients with a history of moderate to severe pain for more than a year were selected. Patients were screened out if they had any physical disability or were getting psychiatric treatment. Besides demographic data, McGill Pain Questionnaire, Coping Strategies Questionnaire and Berlin Social-Support Scales were employed to record the study variables. Age range of patients varied from 25–58 years. All the patients were educated, working and belonged to middle class.

Results: 65 patients (36 females: 29 males) were recruited from the Pain Clinic in 18 months. 78% patients had impaired physical functioning. Perception of pain depended upon the age, sex, amount of perceived social support and contact with the treating doctor. Females frequently employed religious coping (95%) and used self statements (80%); as opposed to males who relied on ignoring the sensations (88%) and increasing behavioural activities (65%).

Conclusion: The study reflected the cultural differences in type of coping strategy employed by a given patient. Female patients were somatically-focused but only 35% met the criteria for Somatization Disorder. Male patients employed techniques that allowed their control on the environment and illness whereas females patients relied on techniques that were passive in nature. Learning to live with a chronic pain is quite challenging for women who are feeling-oriented and look up to men not only to fulfil their needs but to get social approval in the context of Pakistani society.

P 51. A randomised, placebo-controlled study of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with major depressive disorder (MDD)

S. Montgomery¹, A. Cutler², A. Lazarus³, M. Schollin⁴, M. Brecher³

¹Imperial College School of Medicine, University of London, London, United Kingdom, ²Department of Psychiatry, University of Florida, Florida, USA, ³AstraZeneca Pharmaceuticals Wilmington, USA, ⁴AstraZeneca R&D, Södertälje, Sweden

Background: To evaluate the efficacy and tolerability of once-daily quetiapine XR (extended release) monotherapy in patients with MDD (unipolar depression) compared with placebo.

Methods: 8-week (6-week active treatment, randomised phase; 2-week post-treatment drug-discontinuation/tapering phase), multicentre, double-blind, randomised, parallel-group, placebo- and active-controlled study (D1448C00002). Patients were randomised to quetiapine XR 150mg/day, 300mg/day, duloxetine 60mg/day (active-control) or placebo. Primary endpoint: change from baseline to Week 6 in MADRS total score. Secondary variables included: change from baseline starting at Day 8 in MADRS total score, MADRS response ($\geq 50\%$ reduction in score from baseline) and remission (MADRS total score ≤ 8) at Week 6. Adverse events (AEs) were recorded throughout the study.

Results: 612 patients were randomised: 152 quetiapine XR 150mg/day, 152 quetiapine XR 300mg/day, 151 duloxetine, 157 placebo.

Mean MADRS total score (overall baseline mean, 30.15) was significantly reduced at Week 6 by quetiapine XR 150mg/day, 300mg/day and duloxetine versus placebo (-14.81 , -15.29 , -14.64 , -11.18 , respectively; $p \leq 0.001$). At Day 8, mean MADRS total score was significantly reduced by quetiapine XR 150mg/day (-8.36 , $p < 0.01$) and 300mg/day (-8.19 , $p < 0.01$) versus placebo (-6.01), but not duloxetine (-6.81 , $p = 0.3$).

At Week 6, response rate was significantly higher for quetiapine XR 150mg/day (54.4%, $p < 0.01$), 300mg/day (55.1%, $p < 0.01$) and duloxetine (49.6%, $p < 0.05$) versus placebo (36.2%). Remission rate was significantly higher for quetiapine XR 300mg/day (32.0%, $p < 0.05$) and duloxetine (31.9%, $p < 0.05$) versus placebo (20.4%), but not quetiapine XR 150mg/day (26.5%, $p = 0.3$).

During Weeks 1–6 the most common AEs ($> 10\%$) were: dry mouth (33.6, 38.2, 18.8, 8.9%), sedation (38.8, 36.8, 16.1, 5.1%), somnolence (24.3, 27.0, 12.8, 7.0%), dizziness (14.5, 19.1, 16.8, 10.8%), headache (10.5, 9.2, 18.1, 10.2%), constipation (5.9, 8.6, 11.4, 6.4%), nausea (10.5, 5.3, 36.2, 9.6%), diarrhoea (4.6, 2.6, 10.7, 6.4%) and insomnia (1.3, 1.3, 14.8, 7.0%) with quetiapine XR 150mg/day, 300mg/day, duloxetine and placebo, respectively.

Conclusion: Quetiapine XR monotherapy at 150 and 300mg/day was effective and well tolerated in MDD, with onset of response as early as Day 8.

P 52. Search for medical treatment and comorbidity of chronic medical disorders and somatoform disorder with bipolar spectrum subgroups in a population-based sample of Sao Paulo

D. Moreno¹, L.H.S. Andrade²

¹Mood Disorders Unit, School of Medicine, ²Psychiatric Epidemiology Unit, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil

Background/aims: The bipolar spectrum and its medical comorbidities are poorly studied in communities. In the present study, the sample of the Sao Paulo Epidemiologic Catchment Area Study (ECA-SP) yielded a weighted lifetime prevalence of 8.3% for the bipolar spectrum (CIDI 1.1/ DSMIII-R). Epidemiological studies point to a lack of search for mental health treatment in bipolar disorders, but a high use of medical services. The aims of this study are to compare the lifetime association of bipolar spectrum subgroups and non-affective controls (NAC), and of classes of subjects yielded through latent class analysis (LCA), with cardiovascular disorders (CVD), diabetes, cancer, asthma, and somatoform disorder, and to determine differences in the rate of search for medical help between these groups in the month prior to the interview.

Methods: Data from the ECA-SP sample ($N = 1,464$; 18 years old) were analyzed and self-reported medical comorbidities in the month prior to interview, somatoform disorder, and search for medical services of NAC compared to four BP spectrum subgroups ($N = 122$), originated either from the DSMIII-R (BP I and BP II), or from the CIDI 1.1 manic syndrome. Also, a LCA was applied to CIDI manic and depressive symptoms. Logistic regression models were adjusted to examine associations and odds-ratios calculated.

Results: Search for help and somatic/medical suffering was significantly and increasingly more prevalent in more severe BP groups, mainly asthma (66% in BP I+BP II) and CVD (59% of BPI+BP II), whereas somatoform disorder occurred almost exclusively in BP groups. LCA showed greater frequency of CVD and somatoform disorders in more severe bipolar and depressive classes, whereas asthma was more prevalent in bipolars.

Conclusion: Somatic/medical suffering is prevalent mainly in BPI and BP II, but also in bipolar spectrum subjects, as well as in bipolar and depressive classes, leading to high medical costs and suffering, what are in opposition to the lack of adequate psychiatric diagnosis and treatment.

P 54. Efficacy of Pregabalin and Venlafaxine-XR in Generalized Anxiety Disorder: Results of a Double-Blind, Placebo-Controlled 8-Week Trial (A0081012)

T. K. Murphy, G. Nivoli, A. Petralia, F. Mandel, T. Leon

Pfizer Global Pharmaceuticals, Pfizer Inc, New York, NY, USA

Objective: Efficacy has been demonstrated for several classes of drugs in the treatment of generalized anxiety disorder (GAD) based on double-blind, placebo-controlled trials. However relatively few head-to-head comparator trials in GAD have been reported. The objective of the current study was to

evaluate the comparative speed of onset of anxiolytic activity, and the overall anxiolytic efficacy of pregabalin (PGB) and venlafaxine-XR (VXR) in patients with GAD.

Methods: This was a double-blind trial in which adult outpatients, ages 18–65 years old, who met DSM-IV criteria for GAD, with a HAM-A total score ≥ 20 , were randomized to 8-weeks of flexible-dose treatment with PGB (300–600 mg/d), VXR (75–225 mg/d), or placebo (PBO). The primary outcome was last observation carried forward (LOCF) endpoint change in HAM-A total score.

Results: The intent-to-treat sample consisted of 121 patients on PGB (64% female; mean ($\pm$ SD) age, 39.5 ± 11.9 years; mean ($\pm$ SE) baseline HAM-A, 27.6 ± 0.4 ; baseline CGI-Severity, 4.74 ± 0.7), 125 patients on VXR (58% female; age, 42.6 ± 11.8 years; baseline HAM-A, 27.4 ± 0.4 ; CGI-S, 4.78 ± 0.7), and 128 patients on PBO (61% female; age, 40.2 ± 12.1 years; baseline HAM-A, 26.8 ± 0.4 ; CGI-S, 4.66 ± 0.7). Treatment with PGB was associated with a significantly greater LS mean change in the HAM-A total score at LOCF-endpoint vs. PBO (-14.5 ± 0.9 vs. -11.7 ± 0.9 ; $P=0.028$). Treatment with VXR was not significant vs. PBO at endpoint (-12.0 ± 0.9 ; -11.7 ± 0.9 ; $P=0.968$). Treatment with PGB showed an early onset of improvement, with significantly greater LS mean change in the HAM-A by day 4 vs. both PBO ($-5.3 \pm .5$ vs. -3.4 ± 0.5 , $P=0.008$) and VXR (-2.9 ± 0.5 ; $P=0.0012$). The CGI-Severity score was significantly more reduced at LOCF-endpoint on PGB vs. PBO (-2.02 ± 0.2 vs. -1.52 ± 0.2 , $P=0.019$). Endpoint change in CGI-S was not significantly different than PBO on VXR (-1.67 ± 0.2 ; $P=0.36$). The proportion of patients reporting any severe adverse event was similar for PGB (9.1%) and PBO (7.8%), but somewhat higher for VXR (20.0%). Premature discontinuation due to adverse events was higher on both PGB (12.4%) and VXR (17.6%) compared to PBO (5.5%).

Conclusions: Pregabalin was a safe and effective treatment of GAD, with a significantly earlier onset of anxiolytic activity than venlafaxine-XR. The failure of venlafaxine-XR to demonstrate significant efficacy versus placebo appears to be attributable to a relatively high placebo response in the current study.

Supported by Pfizer Inc.

P 55. Regulating negative moods through affect, behavior, cognitive, and social strategies

J. Overholser, A. Marquart, N. Peak
Case Western Reserve University, Cleveland, USA

Aim: The present study was designed to evaluate patient expectations regarding their ability to manage their negative emotional reactions, examining affect regulation, behavioral activation, cognitive

restructuring, and social involvement as strategies for managing negative emotional reactions.

Method: 144 adult psychiatric inpatients were evaluated using a structured diagnostic interview and several established questionnaires. All patients were diagnosed with a mood disorder according to DSM-IV criteria (American Psychiatric Association, 2000), and the diagnosis was supported by SCID structured diagnostic interview (First, Spitzer, Gibbon, & Williams, 1995). All patients completed measures of depression severity (Beck Depression Inventory, Beck et al., 1961), hopeless attitudes (Beck Hopelessness Scale, Beck et al., 1974), suicide risk (Beck Scale for Suicidal Ideation, Beck & Steer, 1991), and expectations regarding mood regulation (Negative Mood Regulation Scale, Catanzaro, 1994).

Results: Depressed psychiatric inpatients reported weak expectations regarding their ability to regulate their negative moods. Patient expectations regarding behavioral activation strategies were strongly correlated with more severe depressive symptoms ($r=-.498$, $p<.001$) and higher levels of hopelessness ($r=-.509$, $p<.001$). Patient reliance on affect regulation strategies was related to higher levels of hopelessness ($r=-.517$, $p<.001$), and more frequent suicidal thoughts ($r=-.366$). Few differences were found between suicidal and non-suicidal depressed inpatients on any measure. However, among patients diagnosed with chronic depression, negative mood was strongly correlated with poor social functioning ($r=-.877$, $p<.001$) and inadequate cognitive attitudes ($r=-.603$, $p<.001$).

Conclusions: Depression severity, chronicity, and suicide risk are closely related to patients' expectations regarding the ability to control negative moods through affect, behavior, cognitive, and social actions. Therapy may help to develop a range of coping options that patients can use to reduce their depressive tendencies. It may be useful to assess patient expectations in order to guide therapy toward affect regulation, behavioral activation, cognitive restructuring, or social involvement strategies.

P 57. An assessment of Drug-Drug interaction: the effect of desvenlafaxine succinate and Duloxetine on the pharmacokinetics of desipramine in healthy subjects

A. Patroneva¹, S. Connolly², P. Fatato¹, A. Nichols¹, J. Paul¹, C. Guico-Pabia¹

¹Wyeth Research Collegeville, PA, USA, ²Centra State Medical Center Freehold, NJ, USA

Background: A number of antidepressants, including duloxetine, inhibit the cytochrome P450 (CYP) 2D6 enzyme system, which can lead to drug-drug interactions (DDIs). However, desvenlafaxine succinate (DVS) is not expected to inhibit CYP2D6 activity.

Methods: This single-center, randomized, open-label, 4-period, crossover study was designed to evaluate the effects of multiple doses of DVS (100mg/d) and duloxetine (30mg twice-daily) on the pharmacokinetics (PK) of single-dose CYP2D6 probe desipramine (50mg). Participants with genetic polymorphisms that impact CYP2D6 metabolism were excluded. On study day 1 single dose desipramine was administered, followed by multiple daily doses of DVS or duloxetine (days 6–14). On day 11 another single dose of desipramine was administered. Blood samples for PK analyses were collected for up to 120 hours after the final dose of test article for determination of desipramine and 2-hydroxydesipramine plasma concentrations. After a 5-day washout phase, the alternate agent (either DVS or duloxetine) was administered in the same manner as the previous phase. Cmax and AUC were compared between therapies using ANOVA.

Results: Of the 47 individuals initially screened, 20 were enrolled. Two subjects who were predicted not to be CYP2D6 extensive metabolizers were excluded from the sensitivity analysis. Desipramine plasma concentrations (AUC and Cmax) were significantly greater after duloxetine administration than after receiving DVS ($P < 0.001$). Conversely, the Cmax for 2-hydroxydesipramine levels were significantly lower after duloxetine administration than after DVS ($P < 0.001$); differences in AUC did not reach statistical significance ($P = 0.054$). Eleven adverse events were reported following duloxetine administration and 9 were reported after administration of DVS. Headache, the most frequently reported treatment-emergent adverse event, was reported by 40% of subjects overall, by 35% of subjects receiving duloxetine and by 23.5% receiving DVS.

Conclusions: Duloxetine significantly affected plasma concentrations of desipramine and its active metabolite 2-hydroxydesipramine, suggesting a risk for CYP2D6 mediated DDIs. Conversely, DVS did not have a significant effect on the PK of desipramine, which indicates a lower risk for CYP2D6 DDIs.

P 58. Searching Susceptibility Loci for mania: a Sib pairs pilot study

A. Pirovano, C. Lorenzi, D. Dotoli, F. Buongiorno, E. Marino, M. Catalano, E. Smeraldi
Ospedale San Raffaele, Università Vita-Salute, Milan, Italy

Background: Mood disorders are one of the most important cause of disability for human health and the second leading source of disease burden, going beyond cardiovascular diseases, dementia, lung cancer, and diabetes. Numerous reviews demonstrated the main role of genetic factors, in determining

susceptibility to mood disorders, in particular to bipolar ones.

In fact, thanks to a plenty of linkage studies, several candidate chromosomal regions were identified. Nevertheless, none of past genetic studies truly focuses on the genetic basis of mania, which is the “core” clinical constituent of bipolar disorders.

The present research project aimed to localize molecular areas of human genome, responsible for susceptibility to manic facets of bipolar disorders.

Methods: Our whole sample consisted of 177 Italian sib pairs of subjects affected by mood disorders and, when available, their healthy sibs.

DNA samples were initially genotyped with 32 simple tandem repeat markers, on chromosome 12 and 13, showing an average heterozygosity of 0.79 and an average marker density of 10 centimorgans (cM). We performed a non-parametric linkage analysis by the program QTL express. Samples of two or more siblings can be analyzed for linkage using a variance approach, because siblings that inherit more QTL alleles identical-by-descent (IBD) tend to be more similar in phenotype. Hence the difference between their phenotypes tends to be smaller the more QTL alleles they share IBD.

Results: This approach allowed us to identify a region of significant linkage (Approximate LOD: 5.215) between the marker D12S85 (63cM from p-ter of chromosome 12) and manic manifestations of bipolar disorder.

Conclusions: Our finding suggested that specific genetic factors for mania exist. We could assume that manic facets, acting in synergy depressive ones, could end in bipolar disorders.

Our findings, even if very preliminary, could be useful in clinical practice; in fact, in relation to genetic pattern of the single subjects, we could presume the time course of bipolar disease.

P 59. Desvenlafaxine succinate versus Placebo for prevention of depressive relapse in adult outpatients with major depressive disorder

B. Pitrosky¹, K. Rickels², S. Montgomery³, K. Tourian⁴, J.D. Guelfi⁵, S.K. Padmanabhan⁴, J.M. Germain¹, C. Leurent¹, C. Brisard¹

¹Wyeth Research Paris, France, ²University of Pennsylvania, Philadelphia, PA, USA, ³Imperial College School of Medicine London, United Kingdom, ⁴Wyeth Research Collegeville, PA, USA, ⁵CCME, Centr. Sainte-Anne, Univ. Paris V, Paris, France

Objectives: The majority of patients with major depressive disorder (MDD) experience a recurrence after recovery from an index episode of depression. Risk of future depressive episodes increases over time, and symptoms tend to worsen. This study to compare the efficacy and safety of desvenlafaxine

succinate (DVS) with placebo in preventing relapse of depression in adults with MDD.

Method: This was a phase 3, multicenter, placebo-controlled trial. Outpatients with MDD who had responded (17-item Hamilton Rating Scale for Depression [HAM-D17] total score ≥ 11) to 12-week, open-label DVS therapy (200- or 400 mg/d) were randomly assigned to double-blind (DB) treatment with either DVS (same dose received at the end of the open-label phase: 200- or 400 mg/d) or placebo for 6 months. Patients taking DVS 400 mg/d could have their dose decreased to 200 mg/d for tolerability. The primary end point was time to relapse, defined as a HAM-D17 total score ≥ 16 , Clinical Global Impressions-Improvement score ≥ 6 , or discontinuation due to unsatisfactory response. Time to relapse, measured from DB baseline to first occurrence of relapse, was evaluated using survival analysis (Kaplan-Meier method of estimation) and compared between treatment groups using log-rank tests. Safety assessments included discontinuation rates, treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms, and laboratory tests.

Results: The intent-to-treat population included 374 patients ($n=189$ DVS; $n=185$ placebo) and the safety population included 375 patients ($n=190$ DVS; $n=185$ placebo). Rates of relapse were 42% and 24% in the placebo and DVS groups, respectively. Time to relapse was significantly longer with DVS than placebo (log rank: $P<0.0001$). Rates of discontinuation due to TEAEs were 11% and 18% for DVS and placebo, respectively. The most common TEAEs reported by DVS and placebo patients were headache (27% and 23%), dizziness (15% and 26%), and nausea (15% and 19%).

Conclusions: Treatment with DVS was significantly more effective than placebo in preventing relapse of MDD. DVS was generally safe and well tolerated.

P 60. Social functioning in seasonal affective disorder before and after treatment with duloxetine

E. Pjrek, M. Willeit, N. Praschak-Rieder, A. Konstantinidis, S. Kasper, D. Winkler
Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria

Background: It has been estimated that the seasonal subtype of depression (seasonal affective disorder, SAD) represents about 10% of all subjects with major depression [1]. These figures suggest that SAD is a significant concern for public health, because major depression represents a condition, which affects the patients' ability to function socially and occupationally and is associated with a substantial economic burden. The aim of the present study was to examine social functioning in depressed

SAD subjects before and during treatment with the dual serotonin and norepinephrine reuptake inhibitor duloxetine.

Methods: 26 patients (22 females, 4 males), satisfying the DSM-IV-TR criteria for SAD, were included in an 8 week observational study with open-label duloxetine 60 to 120 mg per day. Ratings with the Social Adaptation Self-Evaluation Scale (SASS) were performed at week 0, 1, 2, 4, 6 and 8. Subjects completed the Sheehan Disability Scale (SDS) and reported the number of days lost due to illness and days with reduction in productivity at week 0 (rating of the month before treatment), week 4 (rating of the first month of treatment) and week 8 (rating of the second month of treatment). Data were analyzed by means of univariate repeated-measures analysis of variance (ANOVA) with Bonferroni corrected post-hoc tests; the $p \leq 0.05$ level of significance (two-tailed) was adopted for all statistical comparisons.

Results: Baseline score on the SASS (32.7 ± 5.9) improved during duloxetine treatment with significance from week 2 on ($p=0.004$) and was as high as 46.5 ± 7.9 at week 8 ($p<0.001$). SDS total score decreased significantly from 20.3 ± 6.1 in the month before treatment to 14.1 ± 5.6 during the first month ($p<0.001$) and 6.0 ± 6.6 during the second month of treatment ($p<0.001$). SDS subscores for work, social life and family life had a similar course over time. At week 0 6.6 ± 6.5 days lost due to illness and 15.8 ± 10.9 days with reduction in productivity were reported for the month before treatment. Days lost due to illness declined to 4.0 ± 6.0 at week 4 ($p=0.090$) and 0.5 ± 1.3 at week 8 ($p<0.001$), whereas days with reduction in productivity decreased to 9.2 ± 8.5 ($p=0.002$) and 3.0 ± 7.5 ($p<0.001$) at the same time points.

Conclusions: Our results indicate that SAD is accompanied by relevant impairment of social functioning, which is in line with prior reports [2]. Treatment with duloxetine leads to improvements in important social domains such as work, social life and family life. Further clinical trials comparing duloxetine with other antidepressants or bright light therapy would be needed to assess potential pharmacoeconomic advantages in the treatment of SAD.

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P 61. Mood symptoms and disorders in association with dietary intake

R. Rintamäki, T. Partonen, J. Haukka, J. Virtamo, D. Albanes, J. Lönnqvist
National Public Health Institute, Helsinki, Finland

Objective: This study examines the association of the intake of omega-3 fatty acids, intake of amino acids and intake of vitamins with mood disorders. Also we studied food consumption and nutrient intake in subjects with mood symptoms.

Methods: A total of 29, 133 men aged 50 to 69 years participated in a population-based trial in Finland. At baseline men completed a diet history questionnaire from which food and alcohol consumption and nutrient intake were calculated. The questionnaire on background and medical history included three symptoms on mental wellbeing, anxiety, depression and insomnia experienced in the past four months. Data on hospital treatments due to a major depressive disorder and mania were derived from the National Hospital Discharge Register, and suicides were identified from death certificates.

Results: We did not find associations between the intake of omega-3 fatty acids, fish consumption and intake of amino acids and depressed mood, major depressive episodes, or suicide. Subjects reporting anxiety or depressed mood had higher intakes of omega-3 fatty acids and omega-6 fatty acids as well as energy. There was no significant association between the dietary intake of vitamins or homocysteine and subsequent admission due to mood disorders.

Conclusions: Dietary intake of omega-3 fatty acids and amino acids showed no association with low mood. Our findings conflict with the previous reports of beneficial effects of omega-3 fatty acids on mood. Further studies are needed to clarify complex associations between the diet and mental wellbeing.

P 62. Subthalamic nucleus deep brain stimulation impact on mood disorders in patients with Parkinson's disease

I. Chereau-Boudet¹, J. Rougier¹, I. De Chazeron¹, P. Derost², M. Ulla², J. Lemaire³, F. Durif², P. Llorca¹
¹Psychiatry Department CHU Clermont-Ferrand,
²Neurology Department CHU Clermont-Ferrand,
³Neurosurgery Department CHU Clermont-Ferrand, Clermont-Ferrand, France

Background: In every day practice, especially motor dimensions are assessed in order to evaluate Parkinson patient's improvement. However, mood is a key concept in Parkinson's recovery understanding. Several cases of transient acute depression or manic symptoms are reported in the literature after bilateral subthalamic nucleus deep brain stimulation in pa-

tients with Parkinson's disease. Respective impact of pre operation mood state and deep brain stimulation frequencies on post operative mood state hasn't been described at our knowledge.

Method: We elaborate a one year prospective study to evaluate mood disorders of twenty Parkinson patients treated by bilateral STN stimulation. Patients were administrated pre and post operative MADRS and Beck scales of depression assessment. Reliability analysis of the both depression scales revealed a significant Cronbach alpha's improvement with suppression of several somatic items. We analyzed respective impact of stimulation frequency used, D-0 mood state, and both the interaction on mood disorders evolution between D-0 and D-360.

Results: Beck scale revealed a sensible amelioration between D-0 and D-360 of five subjects mood disorders. MADRS appeared less sensible instrument assessing only two transitions from a depressive state to an adapted mood balance. Mean variations of mood tone showed congruent results improving depression means for the both scales. This mean amelioration wasn't significant. We created a delta score representing the depression evolution and elaborated with Beck scale (which is the most sensible instrument we used). Linear regressions using delta score like dependant variable revealed none impact of both the initial depression evaluation and the brain stimulation frequency. On the other hand interaction of both the D-0 mood state with the stimulation frequency used indicated a significant effect on the depression state evolution.

Conclusion: Our research illustrates the importance of specific Parkinson's mood measurement instruments. Results about combined effect of deep brain stimulation frequency and initial mood state on depression evolution must be taken into consideration and tested with a more important sample in the future researches.

P 63. Adverse effect from the combined treatment of a manic patient with pharmacotherapy and rTMS

P. Sakkas, C. Theleritis, C. Psarros, T. Paparrigopoulos, G. Papadimitriou
Athens University Medical School, 1st Dept. of Psychiatry, Eginition Hospital, Athens, Greece

Background: This is a report of a jacksonian seizure in a manic patient who was treated at the same time with right prefrontal high frequency rTMS and pharmacotherapy.

Case report: We report the case of a 30-year old female Caucasian patient suffering from type I bipolar disorder (non-psychotic euphoric mania) who was under treatment with quetiapine 600 mg/day, diazepam 20 mg/day and gabapentin 1500 mg/day.

Since the patient did not show any significant improvement with pharmacotherapy [Young Mania Rating Scale (YMRS) score: 28], high frequency rTMS as add-on therapy was performed.

During the second week of combined treatment the patient's condition considerably improved [YMRS score: 9]. Unfortunately, without informing us beforehand, she abruptly discontinued diazepam because she was feeling sleepy. During the ninth session of rTMS she developed a Jacksonian clonic seizure in her left arm and hand which lasted 60 sec. There was no abnormal activity on the EEG both before r-TMS sessions as well as several hours after the seizure. The patient had no history of epileptic seizures and her brain MRI was normal. She started taking diazepam once again and insisted on continuing with the r-TMS treatment. Daily sessions were resumed two days later and completed within ten days-time.

Conclusion: It is proposed that abrupt discontinuation of diazepam may have contributed to the occurrence of this seizure. Patients under treatment with rTMS should never initiate or discontinue any concomitant medication, that could affect convulsive threshold, without notifying first their physicians.

We declare that we have no conflict of interest.

P 64. The PCMAD (Primary Care Mood & Anxiety Diagnoser): the development of a diagnostic tool to Detect SAD, GAD, panic disorder, bipolar disorder and depression

M. Vermani¹, J. Westermeyer¹, M. Stone¹, M. Marcus², M.A. Katzman³

¹Adler School of Professional Psychology, Chicago, USA, ²York University, Toronto, Canada, ³University of Toronto & Northern Ontario School of Medicine, Toronto, Canada

Despite increasing awareness of the abundance of people affected by mood and anxiety disorders, many people go years without receiving an accurate diagnosis or appropriate treatment, resulting in significant risks of morbidity, mortality and huge socio-economic costs (cost of physicians, hospitalizations, and welfare administration). Because access to treatment is often initiated by the family physician, diagnostic tools to overcome limited time and specialty skills may result in improved diagnosis and earlier treatment.

Current structured clinical interviews while theoretically helpful, are often not utilized as they require training and can be quite lengthy and time consuming to conduct. The challenge is therefore to develop a brief, simple diagnostic tool that is easily self-administered and is designed for general practitioners to facilitate the process of screening out anxiety and depression.

The PCMAD (Primary Care Mood & Anxiety Diagnoser) study was undertaken to create a self

administered psychometric tool to effectively detect patients suffering with the Social Anxiety Disorder (SAD), Generalized Anxiety Disorder (GAD), Panic Disorder (PD), Bipolar Disorder (BD) and Major Depressive Disorder (MDD). Subjects were assessed using screening questions from a variety of scales in order to which questions most closely associated with diagnoses made on the clinician administered Mini-International Neuropsychiatric Interview (MINI), 840 primary care patients in across the country agreed to participate in the study, of whom 434 met criteria for SAD, GAD, PD, BD and MDD on the MINI and were administered the screening questions. Results reflected the questions that best correlated with each of the diagnostic groups as a preliminary step in the development of the PCMAD screening tool. Potential value of this tool will be discussed in the poster.

P 65. Escitalopram and duloxetine in the treatment of major depression

A.G. Wade¹, H.F. Andersen², R.W. Lam³

¹CPS Clinical Research Centre, Glasgow, United Kingdom, ²H. Lundbeck A/S, Copenhagen, Denmark, ³University of British Columbia Vancouver, BC, Canada

Purpose: The aim of these analyses was to compare the tolerability and efficacy of escitalopram and duloxetine in the treatment of patients with major depressive disorder over 8 weeks.

Methods: Data from two randomised, multi-centre, double blind studies in specialist [1] or psychiatric and general practice settings [2] were used. The primary efficacy measure in both studies was the MADRS total score.

Results: Patients were randomised to either escitalopram (10–20mg/day) ($n=280$) or duloxetine (60mg/day) ($n=284$). Escitalopram was statistically significantly superior to duloxetine with respect to mean change from baseline in MADRS total score at Weeks 1, 2, 4, and 8 (LOCF). The mean treatment difference at Week 8 was 2.6 points ($p<0.01$). For severely depressed patients (baseline MADRS total score at least 30), a mean treatment difference at Week 8 of 3.7 points ($p<0.01$) was seen. Response to treatment at Week 8 was statistically significantly greater for patients treated with escitalopram, as was remission when defined as MADRS ≤ 10 or 12, but not HAMD ≤ 7 . The percentage of patients that withdrew from the escitalopram group (12.9%, $n=36$) was significantly ($p<0.001$) less than in the duloxetine group (24.3%, $n=69$). Significantly fewer ($p<0.001$) patients withdrew from the escitalopram group due to adverse events (4.6%, $n=13$) than from the duloxetine group (12.7%, $n=36$).

Conclusions: Escitalopram showed advantages in efficacy and tolerability compared to duloxetine in the acute treatment of patients with major depres-

sion. There were additional benefits for escitalopram-treated patients with severe depression.

Disclosure: Drs Lam and Wade have received consultancy honoraria from H. Lundbeck A/S and Forest Laboratories. HF Andersen is an employee of H. Lundbeck A/S.

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P 66. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder

A. Wade¹, K. Gembert², I. Florea²

¹CPS Clinical Research Centre, Glasgow, United Kingdom, ²H. Lundbeck A/S, Copenhagen, Denmark

Purpose: This study evaluated the efficacy and tolerability of escitalopram and duloxetine in the treatment of major depressive disorder (MDD).

Methods: Patients were randomised to 24 weeks of double-blind treatment with fixed doses of escitalopram (20mg) ($n=144$) or duloxetine (60mg) ($n=151$). The primary analysis of efficacy was an analysis of covariance (ANCOVA) of change from baseline to endpoint (Week 24) in MADRS total score (last observation carried forward).

Results: At week 8, the mean change from baseline in total MADRS score was -19.5 for patients treated with escitalopram ($n=143$) and -17.4 for patients with duloxetine ($n=151$), a difference of 2.1 points ($p<0.05$). At week 8, the proportion of responders (at least 50% decrease in MADRS) was 69% (escitalopram) and 58% (duloxetine) ($p<0.05$) and remission (MADRS ≤ 12) rates were 56% (escitalopram) and 48% (duloxetine) (NS). For the primary endpoint, the mean change from baseline in total MADRS score at Week 24 was -23.4 for patients treated with escitalopram and -21.7 for patients with duloxetine, a difference of 1.7 points ($p=0.055$, one-sided). The difference in mean change from baseline in MADRS total score favoured escitalopram at Weeks 1, 2, 4, 8, 12, and 16 ($p<0.05$). The overall withdrawal rates were 22% (escitalopram) and 26% (duloxetine) (NS). The withdrawal rate due to adverse events was lower for escitalopram (9%) compared to duloxetine (17%) ($p<0.05$) and significantly more patients treated with duloxetine reported insomnia (12.6% versus 4.9%) and constipation (8.6% versus 2.8%).

Conclusion: Escitalopram was superior to duloxetine in acute treatment and at least as efficacious and better tolerated in long-term treatment of MDD.

Disclosure: Dr Wade has received consultancy honoraria from H. Lundbeck A/S. K Gembert and I Florea are employees of H. Lundbeck A/S.

P 67. The efficacy and tolerability of duloxetine in fall-winter depression

D. Winkler, E. Pjrek, N. Praschak-Rieder, M. Willeit, A. Konstantinidis, S. Kasper

Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria

Background: Bright light therapy (BLT) has been considered to be the first choice of treatment for patients with seasonal affective disorder (SAD) [1]. However, antidepressant drug treatment is an alternative for patients, who do not respond to BLT or experience side effects [2]. The present study is the first to investigate the clinical usefulness of a dual action antidepressant in SAD.

Methods: 26 outpatients (22 women, 4 men) with the fall-winter type of SAD according to the DSM-IV-TR criteria were included in an 8 week observational study. Subjects received open-label treatment with the dual serotonin and norepinephrine reuptake inhibitor duloxetine in a flexible dosage of 60 to 120 mg. The primary outcome variable was the Structured Interview Guide for the Hamilton Depression Rating Scale (SAD version; SIGH-SAD); secondary outcome parameters included the Clinical Global Impression of Severity (CGI-S), the Clinical Global Impression of Improvement (CGI-I), the CGI Efficacy Index and the UKU Side Effect Rating Scale. Ratings were carried out at week 0, 1, 2, 4, 6 and 8.

Results: SIGH-SAD score at baseline was 33.5 ± 7.4 . Analysis by ANOVA displayed a significant decline of SIGH-SAD from week 1 on ($p=0.007$). At week 8 SIGH-SAD score had further improved to 9.0 ± 12.3 ($p<0.001$). CGI-S score showed a statistically significant decrease from baseline from week 2 onwards ($p<0.001$). CGI-I and CGI Efficacy Index exhibited a similar course over time during the study with significance from week 2 on ($p=0.001$ for both variables). Duloxetine treatment yielded a response rate of 80.8% (SIGH-SAD $< 50\%$ of baseline value) and a remission rate (SIGH-SAD < 8) of 76.9%. 45 adverse events (42.2% mild, 42.2% moderate, 15.6% severe) were documented with the UKU scale during this trial. Most side effects emerged at the beginning of treatment and rapidly subsided during the following weeks. The drop-out rate due to side-effects was 15.4%.

Conclusions: These preliminary results indicate that duloxetine is effective and generally well-tolerated in the treatment of depressed SAD subjects. Further double-blind, randomized, placebo-controlled trials and controlled studies with active comparators are warranted to replicate our results.

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P 68. Changes on subjective estimates of sleep after 6 weeks treatment with olanzapine in acute mania

B. Yoon¹, W-M. Bahk², D-I. Jon³, S-Y. Lee⁴, J-G. Lee⁵, S-H. Won⁶, J-S. Seo⁷, K-J. Min⁸

¹Department of Psychiatry, Naju National Hospital Naju, ²Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, ³Department of Psychiatry, College of Medicine, Hallym University Anyang, ⁴Department of Psychiatry, College of Medicine, Won-Kwang University, Iksan, ⁵ Department of Psychiatry, Dongsuh Hospital, Masan, ⁶Department of Psychiatry, College of Medicine, Daegu Catholic University, Daegu, ⁷Department of Psychiatry, College of Medicine, Konkuk University, Choongju, ⁸ Department of Psychiatry, College of Medicine, Chung-Ang University, Seoul, South Korea

Objective: Some atypical antipsychotics can easily cause sedation and somnolence in the treatment of mania. Such effects sometimes may cause the subjective discomfort of the patients. But there were few studies on the relationship between the sedation and subjective aspects of sleep or daytime sleepiness in bipolar disorder. The aim of this study was to investigate the effect of 6-week olanzapine mono-

therapy on subjective estimates of sleep in patients with acute bipolar disorder.

Method: In a Korean multi-center, open-label, 6-week study, patients with bipolar I disorder were included to treatment with olanzapine. Young Mania Rating Scale (YMRS), Simpson-Angus Rating Scale (SARS) and Barnes Akathisia Rating Scale (BARS) were used to assess the efficacy and side effects. Modified version of Leeds Sleep Evaluation Questionnaire (LSEQ) was used to assess the subjective measures of nighttime sleep and hangover, covering four areas of sleep: i) getting to sleep (GTS), ii) quality of sleep (QOS), iii) awakening from sleep (AFS), and iv) behavior following wakefulness (BFW) or hangover during the next day. All assessments were done at baseline and days 7, 14, 21 and 42 after treatment with olanzapine.

Results: Forty-seven of total 76 patients were completed the study. Changes of YMRS showed significant improvements through the study period. There were no significant differences from baseline in SARS and BARS. While mean changes of GTS, QOS and AFS from baseline were significantly improved at days 7, 14, 21 and 42, those of BFW were not significantly differed between baseline and post-treatment assessments.

Conclusion: Data showed that olanzapine monotherapy had favorable effect on acute manic symptoms and well tolerable. The components affecting nighttime sleep improved after olanzapine treatment, but those related with hangover during the next day did not influenced. This result suggests that olanzapine may improve the self-perceived quality of sleep without any impairment following sleep in acute manic patients.

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International
forum for mental
health research

Journal of **MENTAL HEALTH**



Executive Editor:
Til Wykes,

Institute of Psychiatry, UK

Volume 16, 2007, 6 issues per year

Print ISSN: 0963-8237

Online ISSN: 1360-0567

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Publication Details

Vol. 1, 2008, 4 issues per year

ISSN Print 1931-5864

ISSN Online 1931-5872

2008 Subscription Rates

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