ANXIETY DISORDERS RESEARCH NETWORK (ADRN)

February 2011

Topics

At present, three anxiety disorders form the focus of collaboration: panic disorder, social phobia, and obsessive-compulsive disorder – particularly, important patient groups such as those in the early stages of illness, those with comorbid mental and physical disorders, and those who have not responded to initial treatment approaches.

Main Goal and Aims of the network

Our overall goal is to help address currently unmet needs in anxiety and related disorders, through the development of an independent collaborative European Anxiety Disorders Research Network (ADRN). The specific aims of the ADRN include:

1. developing an independent collaborative network for research into anxiety and related disorders
2. harmonising research and clinical databases and refining research methodologies
3. evaluating innovative interventions, particularly in previously neglected patient groups
4. building a platform for pragmatic randomised controlled effectiveness trials

The burden of anxiety disorders

Anxiety disorders are common, typically have an early onset, run a chronic or relapsing course, cause substantial personal distress, impair social and occupational function, reduce quality of life, increase the risk of suicide, and impose a substantial economic burden. They therefore represent an important public health problem. Many patients with anxiety disorders do not present or are not recognised, the standard of care they receive is often sub-optimal, and the effectiveness of pharmacological and psychological treatment interventions in real-world clinical practice can be disappointing. These represent important clinical challenges, and there is considerable room for improvement in the recognition, care and treatment of patients with anxiety disorders. Despite dedicated research endeavours and some breakthroughs in scientific understanding of neurobiological and psychosocial factors, the causes of anxiety disorders remain largely unknown. This lack of certainty hinders accurate diagnosis, prediction of prognosis, and development of refined treatment approaches.

Anxiety disorders are characterised by considerable cross-sectional and longitudinal co-morbidity with each other and with other conditions such as bipolar disorder, depressive illness, psychosis, substance misuse and a range of physical illnesses. Research findings in study samples from which patients with co-morbid conditions have been excluded may have limited applicability to the overall population of patients seen in wider practice, and hence there is a need to undertake research in fully representative patient groups. Despite the availability of a range of evidence-based pharmacological and psychological treatment interventions, many patients do not respond to treatment, remain troubled by severe symptoms, and endure continuing disability. Comparatively little is known about the determinants of treatment non-response, or the preferable next steps in patient management, after the failure of first-line interventions. Consequently, there is a clear need to undertake research in the substantial proportion of patients with ‘treatment-resistant’ anxiety disorders.

Anxiety disorders often precede the development of depressive disorders and substance misuse problems. In addition, anxiety disorders may increase mortality due to physical illness. However longitudinal epidemiological studies have not established whether the recognition and effective treatment of patients with anxiety disorders reduces the likelihood of their subsequently developing these associated conditions. There is a need to undertake further longitudinal research in clinical populations that are sufficiently large to ascertain whether effective treatment of anxiety can prevent the subsequent appearance of depressive illness or substance misuse.

The need for a European perspective

The European population is large, dispersed widely, ethnically varied, and rich in cultural diversity with differing social and religious traditions. These factors support the conduct of collaborative research activity, which not only investigates biological factors such as genetic variations and neuropsychological observations, but also considers the effects of culture and upbringing, and the variation in health care systems. There are of course many world-leading centres of excellence with dedicated and productive research units within Europe, some with substantial clinical and research databases, large and detailed enough to have already contributed to ground-breaking insights into anxiety disorders. However, different centres have often employed differing methodologies, and this variation reduces the ability to confirm or refute new findings across centres, particularly in smaller samples. We believe there
is considerable scope to facilitate the development of a multi-centre collaborative joint patient database, to harmonise research methodologies across centres, and to bring a European perspective to the current debate around internationally accepted diagnostic criteria for anxiety disorders.

The need for an independent research network
Research into anxiety disorders within Europe generally attracts less funding from major international grant-giving bodies than is awarded to other mental disorders or neurodegenerative conditions, and is more reliant upon support from local medical charities and industrial partners such as pharmaceutical companies. This reliance can affect the identification of research priorities and the development of collaborative endeavours that address the most important areas of unmet clinical need. These difficulties would be reduced through the development of an international and collaborative research network, which supports the identification of research priorities and aims to improve clinical outcomes in patients with anxiety disorders. This would facilitate the harmonisation of research and clinical databases and support the refinement of research methodologies. Through these activities, this network should contribute to greater accuracy in the prediction of clinical outcome, and would encourage the evaluation of innovative interventions, particularly in important patient groups such as in the early stages of illness, those with comorbid mental and physical disorders, and those who have not responded to initial treatment approaches.

General Methods Used
Research priorities for the ADRN are reached through group consensus. Phased collaborative research projects are planned in panic disorder, social phobia, and obsessive-compulsive disorder (OCD). These disorders were selected primarily to align with the interests, experience and expertise of ADRN members, but also because it is important to compare a disorder characterised by unexpected panic attacks with one in which panic attacks occur only expectedly; and to compare these disorders with OCD, in which panic attacks are unusual, and which lies on the outer margins of the anxiety disorders.

Ideas for innovative investigations include characterising differing endophenotypes across diagnoses; using neuroimaging, genetic polymorphism analysis, and psychological and pharmacological challenge techniques to bridge the gap between preclinical and clinical studies; and investigation of the neurobiological correlates of the response to psychological interventions. Other potential endeavours include conducting case-controlled investigations of anxiety disorder patients with or without co-morbid depressive or substance use disorders; identifying predictors of clinical outcome and treatment response using dimensional and other approaches; and establishing a wide platform to support pragmatic randomised effectiveness trials in patients with resistant illnesses. Further ideas will be developed in consultation with representatives from relevant international user and carer organisations.

Description of the main studies implemented

1. Publication of the ADRN ‘manifesto’
A ‘manifesto’ was developed in order to summarise the rationale, aims and objectives for the ADRN, and was published in European Neuropsychopharmacology in 2010. The manifesto highlights the need for an independent European collaborative research network, summarises our intended activities, and serves to attract potential participants towards our collaborative projects.

2. The EUSARNAD study
Background
The ‘EUSARNAD’ study (full name: Joint European and South African Research Network in Anxiety Disorders) is a proposal to the European Commission, through the Marie Curie Actions (People) International Research Staff Exchange Scheme, and is designed to build on the strengths of the ADRN and to extend these by establishing firmer research collaboration with the University of Cape Town in South Africa. Through establishing this research exchange, we aim to share knowledge and expertise among participating centres, in order to ensure a comprehensive translational research approach in anxiety disorders, relevant to the needs of developed and developing societies. This proposal has three aims: first, to allow South African researchers to gain detailed first-hand experience of certain research methodologies in European centres; second, to help European investigators gain access to and greater understanding of the origin of anxiety disorders and problems in their management within an emerging country, and third, to thereby enhance the relevance of translational research activity jointly conducted within Europe and South Africa to other developed and developing societies.

Aims of the study
The proposed exchange scheme has three broad objectives. First, to develop a collaborative international database for the detailed characterisation of the clinical and other characteristics of large patient samples, across the range of
anxiety disorders. Second, to provide the exchange researchers with a range of training opportunities and for them to gain experience in innovative investigations in anxiety disorders. These opportunities will be spread across the range of participating centres, and currently include the characterisation of differing endophenotypes across diagnoses; using neuroimaging, genetic polymorphism and other techniques to bridge the gap between preclinical and clinical studies; and identifying predictors of clinical outcome and treatment response using dimensional and other approaches. The third objective is to establish a firm platform to support subsequent pragmatic randomised effectiveness trials in patients with anxiety disorders who have not responded to previous pharmacological or psychological treatment interventions.

**Progress of the study**

The proposal for the EUSARNAD study scored 86.4/100 in the first round and was graded ‘A’ in the second, indicating that the Commission wishes to fund the scheme. The proposal successfully completed the ‘negotiation’ phase with the Commission in January 2011, and is currently being considered by the Commission Ethics Review Committee. Progress through the Commission process has been slower than expected, but we expect to start the research exchange scheme this year.

3. The EU-ROCC study

The EU-ROCC study (full name: European Research into Obsessions and Compulsions in Children and Adolescents) investigates paediatric and adolescent obsessive compulsive disorder and pathological gambling, and comprises an integrated interdisciplinary translational research programme, bringing together experts in preclinical animal and human research, with experts in clinical trial design and therapy. Members of the ADRN (Fineberg, Denys, Zohar, Pallanti, Baldwin) are leading applicants in this proposal for research funding to the European Commission, following its call for research proposals in this area (‘HEALTH.2011.2.2.1-3: Addictive and/or compulsive behaviour in children and adolescents: translating pre-clinical results into therapies’). The outline proposal for the EU-ROCC study was successful, and the full proposal was submitted to the Commission in February 2011. If funded, through Work Package 8 (led by the ECNP President Professor Zohar), the ADRN would take a leading role in dissemination and training, and in developing communications about the scope of the study and its findings, to both a scientific audience and the general public. As part of the anticipated costs for this Work Package, a contribution towards the salary of the part-time ADRN administrator is being sought.

4. Publication of the textbook, ‘Stress and Anxiety Disorders’

As part of its ‘Trends in Pharmacopsychiatry’ series, Karger publishers have commissioned the ADRN Chair to edit a textbook called ‘Stress and Anxiety Disorders’, with contributions from ADRN members, to provide a state-of-the-art compendium of what is known, and what remains unknown, about the treatment of anxiety disorders. This is due for publication early in 2012, and will highlight the support of the ECNP and ECNP-NI, in facilitating the development of the ADRN.

**Worksteps**

Three phases of collaboration and network development are envisaged, for the ADRN ‘project’. Phase I comprises development of a common database of demographic, clinical and familial characteristics, focusing on cross-sectional measures of symptom severity and ‘co-syndromology’, together with longitudinal characteristics such as duration of symptoms and disorders, and record of previous interventions. Phase II of ADRN collaboration would see the pooling of genetic data (from patients with anxiety disorders and possibly their first-degree relatives), and evaluation of the results of simple treatment interventions. Phase III is envisaged to include more complex investigations, such as neuroimaging studies and psychological or pharmacological challenge tests.

Initial support for some aspects of Phase I has been provided through the ECNP-NI, largely funding for a part-time administrative assistant (Miss Catherine Carr, working 0.2 WTE) to support the Professor Baldwin, and based in Southampton. Miss Carr played a pivotal and commended role in coordinating the submission of the EUSARNAD study, and also facilitated the development of the early stages of the EU-ROCC study. Financial and administrative support for Phases II and III is reliant upon application to major European grant agencies, as has been undertaken through the EUSARNAD and EUROCC studies.

**Timelines for the next 12 months**

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<tr>
<td>10th February 2011</td>
<td>Full EU-ROCC proposal submitted.</td>
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<tr>
<td>26th March 2011</td>
<td>ADRN session in Anxiety Disorders Association of America, New Orleans, USA.</td>
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<tr>
<td>24-25th May 2011</td>
<td>Meeting during International Anxiety Disorders Symposium, Amsterdam.</td>
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May 2011  Start of collaborative project linking Leiden and Southampton.

June 2011  EUSARNAD exchange scheme likely to commence.


September 2011  Start of collaborative project linking Milan and Santander.

Continuing activities:
To February 2012  Development of online collaborative database
To February 2012  Development of ADRN website and blog
To February 2012  Development of ADRN 'lay expert panel'

Outcome and results already obtained
March 2010  Submission of EUSARNAD study to EU Commission
June 2010  Publication of ADRN manifesto in European Neuropsychopharmacology
July 2010  Feedback from Commission on EUSARNAD study
November 2010  Submission of revised version of EUSARNAD study to EU Commission

February 2011  Submission of full version of EU-ROCC study to EU Commission

Deliverables

1. Increased awareness of the ECNP-NI and ADRN through presentations at scientific meetings
   The role of the ECNP and ECNP-NI in supporting independent collaborative research into the causes and treatment of anxiety disorders, particularly in groups of patients that have often been overlooked, will be highlighted through ADRN-linked sessions at the following meetings.
   b. Anxiety Disorders Association of America, New Orleans, March 2011. Professors Allgulander and van der Wee and Dr Davies are all speaking in session 336 ‘Patients, primary care and policies – a view from across the pond’ on 26th March.

2. Collaborative research into determinants of vulnerability and resilience
   The ECNP-NI previously approved (March 2010) funding for two preliminary studies, relating to genetic determinants of vulnerability and treatment response, with an emphasis on corticoid receptor variability (van der Wee, Maron); and into elucidating vulnerability and resilience to stress (van der Wee, Baldwin). Providing funding pledged for 2010 can be carried over into the next twelve months, these projects will be undertaken between May 2011 and February 2012. The nature of the two projects is summarised below.

3. Development of a questionnaire for assessment of the onset of illness and latency to treatment
   Following the ADRN meeting at the 2010 ECNP Congress, a proposal for funding of the development of a novel and specific questionnaire which would facilitate investigation of the effects of duration of untreated illness in anxiety disorders (led by Altamura and Dell'Oso, with input from Vazquez-Barquero and Herran) was considered suitable for our collaboration, and we wish to undertake this work, in the next twelve months. The nature of this project is summarised below.

4. Development of a 'lay expert panel' for research in anxiety disorders
We intend to develop a suitable ‘lay expert panel’ of representatives from patient self-help organisations, linked to some ADRN centres, to guide development of future research proposals and to facilitate dissemination of research findings to as wide an audience as possible.

Proposed projects for 2011-2012

The EUSARNAD and EU-ROCC studies would represent the major areas of collaborative research activity involving ADRN members. If successful, these would be funded by the EU Commission. In addition, we wish to strengthen the network through a range of measures; to carry over the investigation into vulnerability and resilience, which links Leiden and Southampton; and to undertake a preliminary investigation into the effects of untreated illness on clinical outcomes, that would link Milan and Santander.

1. Strengthening the ADRN through continued administrative support

The ADRN has already benefited from ‘pump priming’ funding from the ECNP, through the ECNP Network Initiative. This funding has been largely used to support the salary of an administrator (Catherine Carr), based in Southampton. The administrator ensures good communication between ADRN members, and has played a pivotal role in the development of the EUSARNAD study and a supporting role in coordinating activities leading to submission of the EUROCC study. In addition, the administrator has developed the online computerised collaborative database to be used for future studies involving ADRN members. This includes sections relating to demographic and clinical characteristics and scores on psychopathological rating scales and questionnaires, and ensures that information can be entered readily across centres, whilst preserving patient confidentiality. Current funding for the ADRN administrator continues until February 2011. If funding for the ADRN administrator (0.2 WTE, between March 2011 and February 2012) is continued, the online computerised database could be extended, and an ADRN website could be developed, with an interactive ‘blog’. The ADRN administrator would also have a role in identifying representatives from self-help organisations, to become members of the lay expert panel.

2. ADRN representation at the ADAA meeting, New Orleans, 26th March 2011

Three ADRN members are speaking in Session 336 at the Anxiety Disorders Association of America conference in New Orleans. The session highlights the ADRN and ECNP-NI, and the participation of Christer Allgulander, Nic van der Wee and Simon Davies in the meeting provides an opportunity for these ADRN members to help develop further research and policy-shaping collaborations with like-minded colleagues and representatives of service user organisations from beyond Europe.

3. Collaborative research into determinants of vulnerability and resilience

The ECNP-NI has previously approved funding for preliminary studies relating to determinants of vulnerability and resilience following traumatic events treatment response, with an emphasis on corticoid receptor variability (van der Wee, Maron) and into elucidating vulnerability and resilience to stress (van der Wee, Baldwin), and it is intended that these will be undertaken in 2011.

In collaboration with the Dutch government the Leiden group has started a national, multidisciplinary, multi-centre project aimed at further elucidating vulnerability and resilience to stress. The project will examine psycho-physiological markers of resilience and vulnerability to (traumatic) stress; risk and protective factors associated with (traumatic) stress reactions; brain responses to stress in resilience and in stress-induced psychopathology; genetic modulation of these mechanisms and its relation with resilience and stress induced psychopathology; and efficacy of novel psychological and virtual reality supported interventions aimed at promoting resilience. The Southampton group has started research into resilience and vulnerability to stress in two projects: one in patients with affective psychopathology with and without life-time trauma and one in groups of healthy volunteers, who experienced lifetime trauma, and with or without PTSD.

a. Two-centre exchange of research staff with an interest in resilience and vulnerability

If funding can be carried over from 2010/11 into the current year, this small project will facilitate the exchange of expertise within the ADRN. Senior researchers from the Southampton and Leiden groups will visit each others’ sites to present and discuss projects on resilience and vulnerability, with a special focus on novel approaches. We will explore possibilities for further collaboration on this topic within the ADRN framework (analyses, grant applications and manuscripts). In this small project we would facilitate the exchange of research expertise within ADRN centres.

b. Genetic determinants of vulnerability and treatment response: corticoid receptor variability

If funding can be carried over from 2010/11 into the current year, this project on corticoid receptor variability would be undertaken by van der Wee, de Rijk, van Noorden (Leiden) and Maron (Tallin). The Leiden group has identified several common genetic variants in the human high affinity mineralocorticoid receptor (MR) and in the low
affinity glucocorticoid receptor (GR): these gene-variants are functional, modulating in vitro transactivational capacity, and modifying neuroendocrine responses to several challenges. The project aims to study the influence of common functional MR and GR gene-variants on vulnerability for depression and anxiety, and treatment efficacy in patients with affective disorders. The feasibility of cooperation and insights derived from this small two-centre collaborative project between two centres, would be used to inform the development of wider multi-centre work within the ADRN. Two already available genotyped samples of patients with affective disorders and controls (N=350 from Leiden, N=600 from Tallinn), all previously assessed with the MINI, would be combined. For a subset of patients details on treatment and outcome are available, and this would be used to examine the influence of polymorphisms on outcome. Only high frequency functional gene-variants would be tested. For the GR-gene, the TthlII1, the NR3C1-1, the Bcl-1 and the A3669G (9b) would be examined; for the MR, the -2 G/C and the I180V would be genotyped.

4. Research into the onset of illness and treatment latency
The aims of this project are 1) to develop a specific, short questionnaire – based on the Psychopathological Onset and Latency to Treatment Questionnaire (POLAT) – for assessment in anxiety disorders (the POLATA); 2) to assess the ability of the questionnaire to effectively and reliably collect information in different anxiety disorders; 3) to collect, analyze, quantify and compare latency to different treatments across anxiety disorders - in particular, major determinants of latency, nature of first contact with clinicians/general practitioners and type of first interventions; and 4) to create a novel instrument to be included among those selected by the ADRN group for collaborative multicentre studies. The questionnaire is intended to be a clinician-administered instrument with two sections, focused on psychopathological onset and on first treatments (latency to medications, psychotherapy, type of first contact, duration, etc...). The questionnaire will be developed in English and administered, in the first stage of the project, to approximately 300 patients of the Dept. of Mental Health of the University of Milan with a DSM-IV-TR diagnosis of Panic Disorder, Social Anxiety Disorder, Panic Disorder, Generalized Anxiety Disorder and Obsessive-Compulsive Disorder, during a brief clinical interview.

The OLQ has been already tested in a population of 150 patients with any psychiatric disorder attending our department, with preliminary encouraging results in terms of accuracy and reliability. Among these patients, a subpopulation of patients with anxiety disorders has been identified and the OLQ-A will be administered to them along with 250 new cases. Analyses on demographic and clinical variables will be performed through chi-square tests for the categorical variables and ANOVA for the continuous ones. Correlations between specific variables (e.g., latency to different treatments in specific anxiety disorders) will be performed through logistic regression. Analyses will be performed through the SPSS, 17th version. A preliminary draft of the questionnaire will be circulated for ADRN approval, and would be administered to the target sample (n=300 subjects with anxiety disorders) within 6 to 9 months. Co-investigators from the Psychiatry Research Unit of Cantabria in Santander will contribute to the project by providing an opinion on the questionnaire design and commenting on interim data. Preliminary analyses will be performed at 100 and 200 interviewed subjects and results will be circulated to the ADRN. In the meantime, under the egida of the ADRN, the questionnaire will be validated and published. A validated version of the questionnaire along with a draft of early results should be available for the ECNP-ADRN meeting in Paris, in September 2011.

Funded activities in 2010-2011
The only funded activity for the period March 2010 to February 2011 was for financial support of the ADRN administrator, working on a part-time basis (0.2 WTE). Funding for two small projects – described above and costed below – had been pledged by the ECNP-NI, but for local administrative reasons (including availability of suitable research staff) these two projects have not yet started. We hope that the ECNP will allow us to carry forward these unspent funds into the period of March 2011 to February 2012.

Funding requested for 2011-2012

1. Strengthening the ADRN through continued administrative support
Based on calculations undertaken by the Finance Department of the Faculty of Medicine at the University of Southampton, the cost of continuing to support the salary of ADRN Administrator on the basis of 0.2 WTE (i.e. 1 day per week) for the period 1 March 2011- 28 February 2012 is €6591.

Anticipated total cost €6591

2. ADRN representation at the ADAA meeting, New Orleans, 26th March 2011
Participation of Nic van der Wee: conference registration €600 (already paid); direct flight from Amsterdam to New Orleans, approximately €1200; convention hotel, €150 per night; anticipated total costs (staying for two nights), approximately €2100. Participation of Simon Davies: Will be working in Cayman Islands at time of ADAA, therefore short-haul flight rather than transatlantic flight. Conference registration 675 US Dollars (approximately €600); flight
from Cayman to Houston, then from Houston to New Orleans, £286 (approximately €330); hotel accommodation 
212 US Dollars (approximately €150) per night, for two nights; anticipated total costs, approximately €1260. 

**Participation of Christer Allgulander:** cost of flights being met elsewhere; conference registration €600; convention 
hotel €150 per night for two nights; anticipated total costs €900.

**Anticipated total cost for participation of Nic van der Wee, Simon Davies and Christer Allgulander €4260**

3. **Two-centre exchange of research staff with an interest in resilience and vulnerability**
Two researchers to travel from Leiden to Southampton, and two from Southampton to Leiden. Costs of four return 
flights between Southampton-Amsterdam; 4 times €180, i.e. €720; hotel costs 4 times €140 per night, each 
exchage being for two nights, i.e. €1120; travel between Amsterdam and Leiden for four research staff, 4 times 
€10, i.e. €40 Euros; travel within Southampton for Leiden-based researchers, 2 times €10, i.e. €20. 

(Carried over from 2010-2011) **Anticipated total cost €1900**

4. **Genetic determinants of vulnerability and treatment response: corticoid receptor variability**
The estimated costs for genotyping (for 6 polymorphisms) in a sample of 950 subjects, together with the cost of 
transport of genetic material amount to approximately €5000. 

(Carried over from 2010-2011) **Anticipated total cost €5000**

5. **Research into the onset of illness and treatment latency**
The estimated costs of undertaking detailed assessment of 300 patients by research assistants, using the novel 
questionnaire (POLATA) and other rating scales, of conducting the interim and final statistical analysis, of reviewing 
the results with the Santander investigators, and of associated research governance procedures, amount to 
approximately €3000. 

**Anticipated total cost €3000**

**Summary of anticipated costs of intended ADRN activity, between March 2011 and February 2011**

Carried over from 2010-2011 (unspent)

1. Resilience and vulnerability research staff exchange €1900
2. Genetic determinants of vulnerability and treatment response €5000

New activities for 2011-2012 (requested)

1. Continued administrative support €6591
2. ADRN representation at ADAA meeting €4260
3. Research into onset of onset of illness onset and treatment latency €3000

David Baldwin, on behalf of the ADRN
February 2011