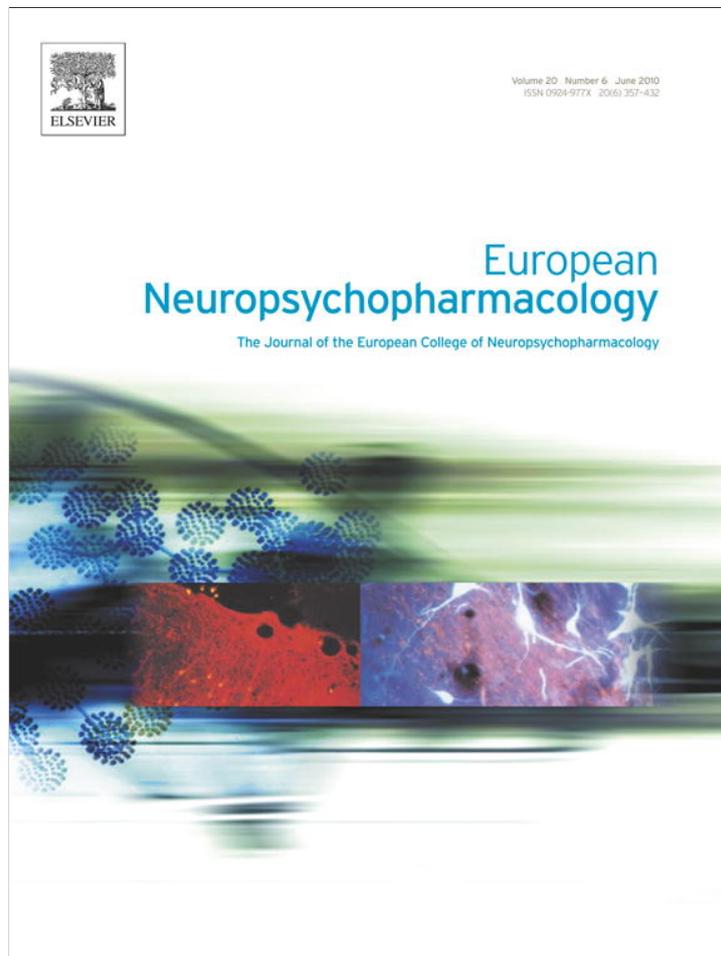


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Manifesto for a European Anxiety Disorders Research Network

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Abstract

Despite the size, burden and costs of anxiety disorders, many patients remain unrecognised, and the effectiveness of evidence-based interventions in routine clinical practice can be disappointing. The European College of Neuropsychopharmacology (ECNP) has established the ECNP Network Initiative (ECNP-NI) to help meet the goal of extending current understanding of the causes of central nervous system disorders, thereby contributing to improvements in clinical

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outcomes and reducing the associated societal burden. The Anxiety Disorders Research Network (ADRN) has been adopted within the ECNP-NI: this consensus statement summarises its overall aims and objectives.

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1. Introduction

A systematic review and pooled analysis of epidemiological studies of mental disorder within European Union countries, conducted on behalf of the European College of Neuropsychopharmacology (ECNP) Task Force on 'Size and Burden of Mental Disorders in Europe' (Wittchen et al., 2005), found that when grouped together anxiety disorders had 12-month and lifetime prevalence rates of approximately 12.0% and 21.1%, respectively (Wittchen and Jacobi, 2005). The anxiety disorders typically have an early age of onset and prolonged course and are associated with reduced quality of life; with the development of psychiatric co-morbidity (particularly for depressive and substance use disorders); and with marked impairment of social and occupational functioning (Wittchen and Jacobi, 2005).

Using these estimates of the prevalence to calculate the size of the population in the European Union that would be affected by anxiety disorders (41 million people, excluding those with post-traumatic stress disorder, for which prevalence estimates may be unreliable), it was estimated that in 2004 anxiety disorders cost in excess of 41 billion Euros (Andlin-Sobocki et al., 2005). It has been argued that increasing the rates of pharmacological treatment in patients with anxiety disorders who are in contact with health services but who are not being treated would be cost-effective, as the increased direct cost of providing treatment would be more than offset by the reduced indirect costs of lost employment, due to the return of people to paid work (McCrone et al., 2008).

Despite the size, burden and costs of anxiety disorders, many patients with these conditions remain unrecognised and the standard of care they receive is usually sub-optimal. Pharmacological and psychological treatments have proven efficacy and generally good acceptability in the context of randomised controlled trials, but the real-world effectiveness of evidence-based pharmacological and psychological treatments in wider patient populations can be disappointing. Furthermore, little evidence exists to guide the further management of patients who have not responded to initial treatments (Allgulander et al., 2003; Baldwin et al., 2005; Bandelow et al., 2008). Although advances in genetics, neuroscience, pharmacology and psychology research have deepened understanding of the neuropsychobiology of anxiety disorders, on an individual basis it is difficult to predict who will become troubled by symptoms; to establish which disturbances of neurotransmitter function underpin those symptoms; and to choose those treatments which would result in optimal clinical outcomes (Baldwin, 2008).

Research into anxiety disorders generally attracts less funding from national grant-giving bodies than is awarded to other mental or neurodegenerative disorders such as schizophrenia, bipolar disorder and dementia. For this reason research into anxiety disorders is often reliant upon

support from the pharmaceutical industry or from small medical charities. There are many world-leading centres with dedicated and productive anxiety disorder research units within Europe, but greater understanding of the neuropsychobiology of the anxiety disorders and the development of improved pharmacological and psychological treatments would undoubtedly be facilitated by the development of an independent supportive collaborative network. Among other activities this would allow sharing of clinical and other databases; refinement of research methodologies; and development and evaluation of innovative treatment approaches, particularly in patients who have not responded to first- and second-line treatments. Furthermore, as has been suggested elsewhere (Maj, 2007), such a network would have a role in lobbying policy makers and in applying to national and European funding bodies for financial support of research studies of clear public health relevance.

The European College of Neuropsychopharmacology (ECNP) is concerned to support the development of independent collaborative international research networks of basic scientists and practising clinicians within Europe, and has established the ECNP Network Initiative (ECNP-NI) to help meet this goal. The aims and activities of its component networks are determined by the experience and expertise of the participating members, but each should have the goal of extending current understanding of the causes of central nervous system disorders, thereby contributing to improvements in clinical outcomes and reducing the societal burden of mental and neurodegenerative disorders. The Anxiety Disorders Research Network (ADRN) was established in 2007 and has been adopted within the ECNP-NI.

2. The ECNP-NI Anxiety Disorders Research Network (ADRN)

Research priorities for the ADRN are reached through group consensus. A 'manifesto' has been developed in order to summarise the rationale for the ADRN. Phased collaborative research projects are planned in three anxiety disorders: namely 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.

Three phases of collaboration and network development are envisaged. 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 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, but support for Phases II and III is reliant upon successful application to major European grant agencies.

Preliminary 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.

3. The ADRN manifesto

- (1) *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. Anxiety disorders therefore represent an important public health problem.*

Anxiety disorders have a 12-month prevalence of approximately 12.0% in the general population aged 18–65 years (Wittchen and Jacobi, 2005). With the exception of generalised anxiety disorder (Lieb et al., 2005) and post-traumatic stress disorder, anxiety disorders typically have an onset in adolescence or early adult life (Horwath and Weissmann, 2000; Goodwin et al., 2005; Fehm et al., 2005) and usually run a chronic or intermittently relapsing course (Bruce et al., 2005; Goodwin et al., 2005; Fehm et al., 2005; Lieb et al., 2005). They have a similar degree of associated disability to that with depressive disorders (Wittchen and Jacobi, 2005) and reduce quality of life markedly (Hoffman et al., 2008; Fehm et al., 2005; Padhi and Fineberg, 2009). Furthermore, they are associated with increased risks of attempted and completed suicide (Sareen et al., 2005; Hawgood and De, 2008) and carry a substantial economic burden (Andlin-Sobocki and Wittchen, 2005).

- (2) *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*

hence there is considerable room for improvement in the recognition, care and treatment of patients with anxiety disorders.

Recognition rates in primary care vary between studies and differing disorders (Baldwin et al., 2005) but may be less good than for depression (Wittchen et al., 2002). Even when recognised it is unusual for recommended treatment to follow evidence-based guidelines (Wang et al., 2000; Stein et al., 2004; Hyde et al., 2005). There is much room for improvement with current pharmacological and psychological treatment approaches: response rates to initial treatment are sub-optimal; it is not possible to predict reliably who will respond well; many patients experience unwanted and distressing adverse effects; others relapse despite continued treatment adherence; and little is known about the further management of patients who do not respond to initial treatments (Baldwin, 2008).

- (3) *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, the prediction of prognosis, and the development of refined treatment approaches.*

Advances in genetics (Finn et al., 2003), neuroendocrinology (Bremner and Charney, 2009), neuropsychology (Ledoux, 1998; Grillon, 2002; Chamberlain et al., 2005), neuroimaging (Sehlmeyer et al., 2009) and temperament research (Rettew and McKee, 2005) have all deepened understanding of the neuropsychobiology of anxiety disorders. However, on an individual level it remains difficult to predict who will become troubled by anxiety symptoms; to establish which neurotransmitter disturbances underpin those symptoms; and to choose the pharmacological or psychological treatments which would result in optimal clinical outcomes.

- (4) *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 clinical practice, and hence there is a need to undertake research in fully representative patient groups.*

There is a high level of co-morbidity between anxiety disorders, and with major depression (Wittchen et al., 2005), bipolar disorder (Henry et al., 2003; Gaudiano and Miller, 2005), schizophrenia (Buckley et al., 2009) substance misuse (Ziedonis et al., 2008; Castle, 2008; Robinson et al., 2009; Crippa et al., 2009) and physical illness (Davies et al., 2007; Roy-Byrne et al., 2008). Co-morbidity is usually regarded as an exclusion criterion in randomised placebo-controlled trials in patients with primary anxiety disorders, where proof of efficacy requires demonstrating that anxiety symptoms do not resolve indirectly, mediated by an effect on another condition. However comorbidity is the rule in routine clinical practice and it is helpful to know whether a single treatment can diminish the severity

of both anxiety and depressive symptoms in patients with comorbid conditions: there is a clear need for further randomised controlled trials in patients with comorbid mood and anxiety disorders (Baldwin and Lopes, 2009).

- (5) *Despite the availability of a range of evidence-based pharmacological and psychological treatment interventions, many patients with anxiety disorders 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. Response rates to acute pharmacological or psychological treatment of anxiety disorders can be disappointing. In addition, many patients do not enter symptomatic remission and remain troubled by persistent residual symptoms and symptom-related disability, which may increase the likelihood of relapse (Choy et al., 2007). Combination and augmentation approaches are helpful in some patients (Hirschmann et al., 2000; Mitte, 2005; Pollack et al., 2006; Hofmann et al., 2006; Skapinakis et al., 2007), but the evidence base for further management of patients who have not responded to initial psychological or pharmacological treatment approaches is limited (Baldwin et al., 2005; Bandelow et al., 2008), and there is a persistent need for studies in patients with refractory anxiety disorders.*
- (6) *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. Despite good evidence that anxiety disorders often precede the development of mood disorders and substance misuse problems (Andrade et al., 2003; Kessler, 2003), it is uncertain whether early intervention for a primary anxiety disorder can reduce the chance of developing subsequent conditions (Altamura et al., 2005; Flannery-Schroeder, 2006; Merikangas and Kalaydjian, 2007). Furthermore, it remains unclear whether treatment of anxiety disorders in patients with physical illness can improve outcome and reduce mortality (Roy-Byrne et al., 2008). There is a need for longitudinal studies in large and representative patient populations, to ascertain whether effective treatment of co-morbid anxiety disorders can improve clinical outcomes in other conditions.*
- (7) *The European population is large, dispersed over a considerable area, ethnically varied, and rich in cultural diversity with differing social and religious traditions.*

These factors support the conduct of collaborative research into anxiety disorders within Europe that 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.

Europe has a population of over 830 million people (of whom 499 million reside in countries within the European Union), spread over 10.2 million km², speaking a multitude of languages. Anthropological research suggests there are 87 distinct peoples of Europe of which 33 form the majority in at least one sovereign state, the remaining 54 peoples being minority ethnic groups, which together comprise approximately 15% of the total population (Pan and Pfeil, 2002). Cultural factors are known to be important in the expression of personal distress and in access to health services (Hinton and Pollack, 2009; Ballenger et al., 2001). The geographic, demographic, linguistic and cultural diversity which characterises Europe therefore makes it fertile ground for investigations of the interactions of genetic, environmental and cultural factors in the origin of anxiety disorders. Furthermore considerable variations in the organisation of primary and secondary care services between countries allow the comparison of differing models of health service delivery.

- (8) *There are 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. Hence, 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.*

In clinical practice, the reliability of psychiatric diagnosis has been improved through use of structured clinical interviews and by reference to internationally agreed diagnostic criteria. In addition, greater awareness of the need to practice 'evidence-based medicine' has reduced some of the variability in treatment delivery. In academic research, many centres within Europe have considerable local case registers and substantial research databases, often extending over long periods. However, as in genetic (Psychiatric GWAS Consortium Coordinating Committee, 2009) and neuroimaging research (Salimi-Korshidi et al., 2009), some standardisation of research methods is needed to permit the accurate comparison and replication of research findings and to allow pooling of data between centres.

- (9) *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.

Funding for research into mental disorders from major grant-giving bodies within Europe has tended to favour research into psychosis, addictions and neurodegenerative disorders (European Union Commission, 2005), and research into anxiety disorders has often relied on funding from other sources. Results derived from industry-supported studies may not necessarily be applicable to wider populations of patients seen in routine clinical practice. For example, the findings of recent large pragmatic randomised controlled trials in complex populations cast a different light on the effectiveness and acceptability of antipsychotic drugs (Naber and Lambert, 2009; Kahn et al., 2008) and antidepressant drugs (Warden et al., 2007), to the findings of randomised controlled trials supported by industry, which are usually designed to support a market authorisation, and conducted in simpler patient groups. The development of an independent international collaborative anxiety disorder research network would support the identification of research priorities based on clinical need, rather than on commercial considerations or local political imperatives.

- (10) *The currently unmet public health, clinical and research needs in anxiety disorders could therefore be addressed by the development of an independent collaborative European Anxiety Disorders Research Network. 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.*

Role of the funding source

The ECNP Network Initiative (ECNP-NI) is supported financially by the ECNP. The Anxiety Disorders Research Network is one component of the ECNP-NI and has received funding from the ECNP-NI to support its initial development.

Contributors

All named authors are members of the ADRN and have contributed to the development of its manifesto, through face-to-face meetings or through exchange of correspondence. David Baldwin is the chair of the ADRN and wrote the draft versions and final version of the submitted manuscript.

Conflict of interest

The ECNP Network Initiative (ECNP-NI) is supported financially by the ECNP. The Anxiety Disorders Research Network is one component of the ECNP-NI and has received funding from the ECNP-NI to support its initial development. David Baldwin is the Chair of the ADRN and makes the following declaration: declarations from the other 18 members of the ADRN do not accompany this manuscript but would be made available upon request.

I do not have shares in any pharmaceutical company, nor do family members. I do not accept any personal retainer from any pharmaceutical company. In the last three years, I have acted as a consultant to a number of companies with an interest in anxiety disorders (AstraZeneca, Eli Lilly, Lundbeck, Pierre Fabre, Pfizer, Roche, Servier, Wyeth). In the last three years I have held research grants (on behalf of my employer) from a number of companies with an interest in affective disorders (Lundbeck, Wyeth), and have accepted paid speaking engagements in industry supported symposia (Astra Zeneca, Lundbeck, Pfizer, Servier) at international and national meetings. I am a medical patron of the self-help organisation charity Anxiety UK.

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References

- Allgulander, C., Bandelow, B., Hollander, E., Montgomery, S.A., Nutt, D.J., Okasha, A., Pollack, M.H., Stein, D.J., Swinson, R.P., World Council of Anxiety, 2003. WCA recommendations for the long-term treatment of generalized anxiety disorder. *CNS Spectr.* 8, 53–61.
- Altamura, A.C., Santini, A., Salvadori, D., Mundo, E., 2005. Duration of untreated illness in panic disorder: a poor outcome risk factor? *Neuropsychiatr. Dis. Treat.* 1, 345–347.
- Andlin-Sobocki, P., Wittchen, H.-U., 2005. Costs of anxiety disorders in Europe. *Eur. J. Neurol.* 12 (Suppl. 1), 39–44.
- Andlin-Sobocki, P., Jonsson, B., Wittchen, H.-U., Olesen, J., 2005. Cost of disorders of the brain in Europe. *Eur. J. Neurol.* 12 (Suppl. 1), 1–27.
- Andrade, L., Caraveo-Anduaga, J.J., Berglund, P., Bijl, R.V., De Graaf, R., Vollebergh, W., Drogomirecka, E., Kohn, R., Keller, M., Kessler, R.C., Kawakami, N., Likic, C., Offord, Ustun, T.B., Wittchen, H.-U., 2003. The epidemiology of major depressive episodes; results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *Int. J. Meth. Psychiatr. Res.* 12, 3–21.
- Baldwin, D.S., 2008. Room for improvement in the pharmacological treatment of anxiety disorders. *Curr. Pharm. Des.* 14, 3482–3491.
- Baldwin, D.S., Lopes, A.T., 2009. The influence of comorbid anxiety disorders on outcome in major depressive disorder. *Medicographia* 31, 126–131.
- Baldwin, D.S., Anderson, I.M., Nutt, D.J., Bandelow, B., Bond, A., Davidson, J.R., den Boer, J.A., Fineberg, N.A., Knapp, M., Scott, J., Wittchen, H.-U., British Association for Psychopharmacology, 2005. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *J. Psychopharmacol.* 19, 567–596.

- Ballenger, J.C., Davidson, J.R., Lecrubier, Y., Nutt, D.J., Kirmayer, L.J., Lepine, J.P., Lin, K.M., Ono, Y., 2001. Consensus statement on transcultural issues in depression and anxiety from the international Consensus group on Depression and Anxiety. *J. Clin. Psychiatr.* 62 (suppl. 13), 47–55.
- Bandelow, B., Zohar, J., Hollander, E., Kasper, S., Möller, H.-J., WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders, Zohar, J., Hollander, E., Kasper, S., Möller, H.-J., Bandelow, B., Allgulander, C., Ayuso-Gutierrez, J., Baldwin, D.S., Buenvicinus, R., Cassano, G., Fineberg, N., Gabriels, L., Hindmarch, I., Kaiya, H., Klein, D.F., Lader, M., Lecrubier, Y., Lépine, J.P., Liebowitz, M.R., Lopez-Ibor, J.J., Marazziti, D., Miguel, E.C., Oh, K.S., Preter, M., Rupprecht, R., Sato, M., Starcevic, V., Stein, D.J., van Ameringen, M., Vega, J., 2008. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders-first revision. *World J. Biol. Psychiatry* 9, 248–312.
- Bremner, J.D., Charney, D.S., 2009. Neural circuits in fear and anxiety. In: Stein, D.J., Hollander, E., Rothbaum, B.O. (Eds.), *Textbook of Anxiety Disorders*, Second edition. American Psychiatric Publishing Inc, Washington, DC, pp. 55–67.
- Bruce, S.E., Yonkers, K.A., Otto, M.W., Eisen, J.L., Weisberg, R.B., Pagano, M., Shea, M.T., Keller, M.B., 2005. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *Am. J. Psychiatry* 162, 1179–1187.
- Buckley, P.F., Miller, B.J., Lehrer, D.S., Castle, D.J., 2009. Psychiatric comorbidities and schizophrenia. *Schizophr. Bull.* 35, 383–402.
- Castle, D.J., 2008. Anxiety and substance use: layers of complexity. *Expert Rev. Neurother.* 8, 493–501.
- Chamberlain, S.R., Blackwell, A.D., Fineberg, N.A., Robbins, T.W., Sahakian, B.J., 2005. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci. Biobehav. Rev.* 29, 399–419.
- Choy, Y., Peselow, E.D., Case, B.G., Pressman, M.A., Luff, J.A., Laje, G., Paizis, M., Ying, P., Guardino, M.T., 2007. Three-year medication prophylaxis in panic disorder: to continue or discontinue? A naturalistic study. *Compr. Psychiatr.* 48, 419–425.
- Crippa, J.A., Zuardi, A.W., Martin-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P., Fusar-Poli, P., 2009. Cannabis and anxiety: a critical review of the evidence. *Hum. Psychopharmacol.* 24, 515–523.
- Davies, S.J.C., Lowry, C.A., Nutt, D.J., 2007. Panic and hypertension: brothers in arms through 5-HT? *J. Psychopharmacol.* 21, 563–566.
- European Union Commission. EU-funded research on mental health. MEMO/05/377 (17/10/2005).
- Fehm, L., Pelissolo, A., Furmark, Y., Wittchen, H.-U., 2005. Size and burden of social phobia in Europe. *Eur. Neuropsychopharmacol.* 15, 453–462.
- Finn, D.A., Rutledge-Gorman, M.T., Crabbe, J.C., 2003. Genetic animal models of anxiety. *Neurogenetics* 4, 109–135.
- Flannery-Schroeder, E.C., 2006. Reducing anxiety to prevent depression. *Am. J. Prevent. Med.* 31 (suppl. 1), S136–S142.
- Gaudiano, B.A., Miller, I.W., 2005. Anxiety disorder comorbidity in bipolar I disorder: relationship to depression severity and treatment outcome. *Depress. Anx.* 21, 71–77.
- Goodwin, R.D., Faravelli, C., Rosi, S., Cosci, E., Truglia, R., de Graaf, R., Wittchen, H.-U., 2005. The epidemiology of panic disorder and agoraphobia in Europe. *Eur. Neuropsychopharmacol.* 15, 435–443.
- Grillon, C., 2002. Startle reactivity and anxiety disorders: aversive conditioning, context, and neurobiology. *Biol. Psychiatry* 52, 958–975.
- Hawgood, J., De, L.D., 2008. Anxiety disorders and suicidal behaviour: an update. *Curr. Opin. Psychiatry* 21, 51–64.
- Henry, C., Van den Bulke, D., Bellivier, F., Etan, B., Rouillon, F., Leboyer, M., 2003. Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. *J. Clin. Psychiatry* 64, 331–335.
- Hinton, D.E., Pollack, M.H., 2009. Introduction to the special issue on anxiety disorders in cross-cultural perspective. *CNS Neurosci. Ther.* 15, 207–209.
- Hirschmann, S., Dannon, P.N., Iancu, I., Dolberg, O.T., Zohar, J., Grunhaus, L., 2000. Pindolol augmentation in patients with treatment-resistant panic disorder: a double-blind, placebo-controlled trial. *J. Clin. Psychopharmacol.* 20, 556–559.
- Hoffman, D.L., Dukes, E.M., Wittchen, H.-U., 2008. Human and economic burden of generalized anxiety disorder. *Depress. Anxiety* 25, 72–90.
- Hofmann, S.G., Pollack, M.H., Otto, M.W., 2006. Augmentation treatment of psychotherapy for anxiety disorders with D-cycloserine. *CNS Drug Rev.* 12, 208–217.
- Horwath, E., Weissmann, M.M., 2000. The epidemiology and cross-national presentation of obsessive-compulsive disorder. *Psychiatr. Clin. N. Amer.* 23, 493–507.
- Hyde, J., Evans, J., Sharp, D., Croudace, T., Harrison, G., Lewis, G., Araya, R., 2005. Deciding who gets treatment for depression and anxiety: a study of consecutive GP attenders. *Br. J. Gen. Pract.* 55, 846–853.
- Kahn, R.S., Fleischhacker, W.W., Boter, H., Davidson, M., Vergouwe, Y., Keet, I.P., Gheorghe, M.D., Rybakowski, J.K., Galderisi, S., Libiger, J., Hummer, M., Dollfus, S., López-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rössler, A., Grobbee, D.E., EUFEST study group, 2008. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 371, 1085–1097.
- Kessler, R.C., 2003. The impairments caused by social phobia in the general population: implications for intervention. *Acta Psychiatr. Scand.* 417, 19–27.
- Ledoux, J., 1998. Fear and the brain: where have we been, and where are we going? *Biol. Psychiatry* 44, 1229–1238.
- Lieb, R., Becker, E., Altamura, C., 2005. The epidemiology of generalized anxiety disorder in Europe. *Eur. Neuropsychopharmacol.* 15, 445–452.
- Maj, M., 2007. The future of academic psychiatry in Europe. *Int. Psychiatry* 4, 53–54.
- McCrone, P., Dhanasiri, S., Patel, A., Knapp, M., Lawton-Smith, S., 2008. *Paying the Price. The cost of mental health care in England to 2026.* King's Fund. ISBN 978 18571175714.
- Merikangas, K.R., Kalaydjian, A., 2007. Magnitude and impact of comorbidity of mental disorders from epidemiologic surveys. *Curr. Opin. Psychiatry* 20, 353–358.
- Mitte, K., 2005. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *J. Affect. Disord.* 88, 27–45.
- Naber, D., Lambert, M., 2009. The CATIE and CUTLASS studies in schizophrenia: results and implications for clinicians. *CNS Drugs* 23, 649–659.
- Padhi, A.K., Fineberg, N.A., 2009. How should we measure health-related quality of life (HR-QoL) in obsessive-compulsive disorder (OCD)? *J. Psychopharmacol.* 23 (suppl.), A33.
- Pan, C., Pfeil, B.S., 2002. *Minderheitenrechte in Europa.* Handbuch der europäischen Volksgruppen. . English translation, 2004.
- Pollack, M.H., Simon, N.M., Zalta, A.K., et al., 2006. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo controlled study. *Biol. Psychiatry* 59, 211–215.
- Psychiatric GWAS Consortium Coordinating Committee Cichon, S., Craddock, N., Daly, M., Faraone, S.V., Gejman, P.V., Kelsoe, J., Lehner, T., Levinson, D.F., Moran, A., Sklar, P., Sullivan, P.F., 2009. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. *Am. J. Psychiatry* 166, 540–556.
- Rettew, D.C., McKee, L., 2005. Temperament and its role in developmental psychopathology. *Harv. Rev. Psychiatry* 13, 14–27.

- Robinson, J., Sareen, J., Cox, B.J., Bolton, J., 2009. Self-medication of anxiety disorders with alcohol and drugs: results from a nationally representative sample. *J. Anxiety Disord.* 23, 38–45.
- Roy-Byrne, P.P., Davidson, K.W., Kessler, R.C., Asmundson, G.J., Goodwin, R.D., Kubzansky, L., Lydiard, R.B., Massie, M.J., Katon, W., Laden, S.K., Stein, M.B., 2008. Anxiety disorders and comorbid medical illness. *Gen. Hosp. Psychiatry* 30, 208–225.
- Salimi-Korshidi, G., Smith, S.M., Keltner, J.R., Wager, T.D., Nichols, T.E., 2009. Meta-analysis of neuroimaging data: a comparison of image-based and coordinate-based pooling of studies. *Neuroimage* 45, 810–823.
- Sareen, J., Cox, B.J., Agifi, T.O., et al., 2005. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population based longitudinal study of adults. *Arch. Gen. Psychiatry* 62, 1249–1257.
- Sehlmeyer, C., Schöning, S., Zwitserlood, P., Pfliederer, B., Kircher, T., Arolt, V., Konrad, C., 2009. Human fear conditioning and extinction in neuroimaging: a systematic review. *PLoS ONE* 10, e5865.
- Skapinakis, P., Papatheodorou, T., Mavreas, V., 2007. Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive-compulsive disorder: a meta-analysis of the randomized controlled trials. *Eur. Neuropsychopharmacol.* 15, 79–93.
- Stein, M.B., Sherbourne, C.D., Craske, M.G., Means-Christensen, A., Bystritsky, A., Katon, W., Sullivan, G., Roy-Byrne, P.P., 2004. Quality of care for primary care patients with anxiety disorders. *Am. J. Psychiatry* 161, 2230–2237.
- Wang, P.S., Berglund, P., Kessler, R.C., 2000. Recent care of common mental disorders in the United States: prevalence and conformance with evidence-based recommendations. *J. Gen. Intern. Med.* 15, 284–292.
- Warden, D., Rush, A.J., Trivedi, M.H., Fava, M., Wisniewski, S.R., 2007. The STAR*D Project results: a comprehensive review of findings. *Curr. Psychiatry Rep.* 9, 449–459.
- Wittchen, H.-U., Jacobi, F., 2005. Size and burden of mental disorders in Europe – a critical review and appraisal of 27 studies. *Eur. Neuropsychopharmacol.* 15, 357–376.
- Wittchen, H.-U., Kessler, R.C., Beesdo, K., Krause, P., Hofler, M., Hoyer, J., 2002. Generalized anxiety and depression in primary care: prevalence, recognition, and management. *J. Clin. Psychiatry* 63 (Suppl. 8), 24–34.
- Wittchen, H.-U., Jonsson, B., Olesen, J., 2005. Towards a better understanding of the size and burden and cost of brain disorders in Europe. *Eur. Neuropsychopharmacol.* 15, 355–356.
- Ziedonis, D., Hitsman, B., Beckham, J.C., Zvolensky, M., Adler, L.E., Audrain-McGovern, J., Breslau, N., Brown, R.A., George, T.P., Williams, J., Calhoun, P.S., Riley, W.T., 2008. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob. Res.* 10, 1691–1715.