Editorial
Άρθρο Σύνταξης

Consequences of major economic crises on citizens' physical and mental health

Psychiatriki 2012, 23:105–108

There have been three major international economic crises during the twentieth century. The great depression, the so-called "financial crash" in 1929, the Russian and Baltic countries economic crisis in 1990 and the East and South-East Asian financial crisis in 1997.

During the "financial crash" there was a fall in international trade of more than 50%, most banks collapsed and unemployment rose rapidly. US policy-markers to mitigate the effects of the depression created a welfare system and invested in public health programs. The package implemented included relief of the unemployment, impoverished farmers, reform of financial regulation and support of wages and prices. Surprisingly, there was evidence that overall mortality in US urban populations fell during the crisis. Especially, there were reductions in mortality from infection diseases (pneumonia, tuberculosis) but concurrently increases in deaths from chronic diseases (heart diseases, cancer, diabetes) and suicide. However, according to recent retrospective epidemiological data, only heart diseases and suicide rate could possibly be directly linked to short-term economic shocks.[1,2]

In 1992, the Russian government started an economic program well known as "shock therapy". Abolition of price control resulted in soaring consumer prices, a rapid decrease in real wages and pensions, a loss of personal savings and a high increase in poverty rate. The next years life expectancy declined by 6 years in men and by 3 years in women. The main causes of death were diseases of the circulatory system and external/violent causes (i.e. suicide, accidents, injury and poisoning). Two principal explanations were proposed for the Russian mortality: stressful socio-economic conditions and heavy alcohol consumption.[3,4]

Baltic countries (Latvia, Estonia, Lithuania) experienced dramatic social-economic upheaval during the same time period. The independence movement of these new states and the rapid transformation of the societies lead to the lost of the State which had taken care for the citizens. There was a rapid increase in poverty, unemployment, divorce rates, general mortality rates and especially suicide. The social changes primarily affected males because of their traditional role to take care of the family's wellbeing and to earn money.[1,3]

In 1997, economic crisis began in Thailand and quickly spread to neighboring economies including Philippines, South Korea, Japan, India, Malaysia and Indonesia. There was an increase in general mortality and especially from suicide in most of the countries. Epidemiological studies conducted suggest that mortality rates were, mainly, associated with the rapid increase in unemployment and decline in household income. It is worth to note that Singapore and Taiwan were less affected by the crisis. This was attributed to the smallest impact of crisis on GDP and unemployment rates.[3–5]

The European economic crisis started in 2008 and has mainly affected the Greek population.[6] Unemployment has risen from 6.6% in 2008 to 22% in 2012 while youth unemployment rose to 45%. Greek Government borrowed from the International Monetary Fund and Eurozone partners under strict conditions that included drastic curtailing of government spendings. As a result, there were cuts in public hospital beds, cuts in health workers and generally in health care spending. In spite of these conditions, an increase in admissions in public hospitals and a decrease in

admissions in private hospitals was recorded. Yet, according to recent data there was an increase in suicide and in attempted suicide, in violence and homicide, in HIV infected people and in heroin users was observed.[7–9]

What can we learn from the experience of the aforementioned economic crises? The main conclusion is that the health impact of the crisis may depend mainly on the dept and length of the crisis and the buffering capacity of a society. Under condition of economic crisis the unemployed, the poor as well as individuals already experiencing a chronic physical or mental disease represent high risk groups for morbidity/mortality or suicide behaviors. In hard times of economic-social crises, the first priority of countries should be the protection of high risk individuals.[1,4,10]

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References

1. Stuckler D, Basu S, Suhrcke D, Cutts A, McKee M. The health implications of financial crisis: A review of the evidence. *Ulster Med J* 2008, 78:142–145
2. Stucker D, Meissner C, Fishback P, Basu S, McKee M. Banking crises and mortality during the Great Depression: evidence from US urban populations 1929–1937. *J Epidemiol Commun Health* 2012, 66:410–419
3. Falagas ME, Vouloumanou EK, Mavros MN, Karageorgopoulos DE. Economic crises and mortality: a review of the literature. *Int J Clin Pract* 2009, 63:1128–1135
4. Uutela A. Economic crisis and mental health. *Curr Opinion Psychiatry* 2012, 23:127–130
5. Chang SS, Gunnell D, Sterne JA, Lu TH, Cheng AT. Was the economic crisis 1997–1998 responsible for rising suicide rates in East/Southeast Asia? All time trend analysis for Japan, Hong-Kong, South Korea, Taiwan, Singapore and Thailand. *Soc Sci Med* 2009, 68: 1322–1331
6. Stuckler D, Basu S, Suhrcke D, Cutts A, McKee M. Effects on the 2008 ressesion on health: a first look on European data. *Lancet* 2011, 378:124–125
7. Keltikelenis A, Katanikolos M, Papanikolas I, Basu S, McKee M, Stuckler D. Health effects of financial crisis: omens of a Greek tragedy. *Lancet* 2011, 378:1457–1458
8. Giotakos O, Tsouvelas G, Kontaxakis V. Suicide rates and mental health services in Greece. *Psychiatriki* 2012, 23:29–38
9. Triantafyllou K, Angeletopolou C. IFM and European co-workers attack public health in Greece. *Lancet* 2011, 378:1459–1460
10. Giotakos O. Financial crisis and mental health. *Psychiatriki* 2010, 21:195–204

Άρθρο Σύνταξης
Editorial

Οι συνέπειες των μεγάλων οικονομικών κρίσεων στη σωματική και ψυχική υγεία των πολιτών

Ψυχιατρική 2012, 23:105–108

Κατά τη διάρκεια του 20ού αιώνα υπήρξαν τρεις μεγάλες παγκόσμιες οικονομικές κρίσεις. Η μεγάλη ύφεση, το αποκαλούμενο «οικονομικό crash» στα 1929, η οικονομική κρίση της Ρωσίας και των χωρών της Βαλτικής το 1990 και η οικονομική κρίση της Ανατολικής και Νοτιοανατολικής Ασίας το 1997.

Κατά τη διάρκεια του οικονομικού crash υπήρξε κατακόρυφη πτώση των διεθνών χρηματαγορών (περισσότερο από 90%), οι περισσότερες τράπεζες κατέρρευσαν και η ανεργία αυξήθηκε κατακόρυφα και ταχύτατα. Στις ΗΠΑ προκειμένου να μετριασθούν οι κοινωνικές επιπτώσεις της ύφεσης εφάρμοσαν ένα προνοιακό σύστημα με επενδύσεις σε προγράμματα δημόσιας υγείας. Η εφαρμογή του προγράμματος περιλάμβανε την κοινωνική και οικονομική στήριξη των ανέργων, τη μεταρρύθμιση και βελτίωση της αγροτικής παραγωγής, την αναθεώρηση-προσαρμογή των οικονομικών εκκρεμοτήτων των πολιτών, την υποστήριξη των χαμηλόμισθων πολιτών-συνταξιούχων και τη προσαρμογή των τιμών των προϊόντων στις ανάγκες των πολιτών. Προς γενική έκπληξη, υπήρξαν σαφείς ενδείξεις ότι η γενική θνησιμότητα στον αστικό πληθυσμό μειώθηκε κατά τη διάρκεια της κρίσης. Ειδικότερα, παρατηρήθηκε μείωση της θνησιμότητας από μολυσματικές ασθένειες (πνευμονία, φυματίωση) ενώ ταυτόχρονα αυξήθηκε η θνησιμότητα από χρόνιες παθήσεις (καρδιαγγειακά νοσήματα, καρκίνος, σακχαρώδης διαβήτης) και αυτοκτονία. Βέβαια, σύμφωνα με τα δεδομένα πρόσφατης αναδρομικής επιδημιολογικής μελέτης, μόνο οι καρδιαγγειακές παθήσεις και οι αυτοκτονίες θα μπορούσαν να αποδοθούν στις άμεσες βραχυχρόνιες συνέπειες της οικονομικής κρίσης.[1,2]

Στα 1992, η Ρωσική κυβέρνηση εφάρμοσε ένα οικονομικό πρόγραμμα, γνωστό ως "shock therapy". Η απόλυτη και ξαφνική κατάργηση του ελέγχου στις τιμές των προϊόντων οδήγησε σε κατακόρυφη αύξηση των τιμών τους, ενώ παράλληλα η μείωση των μισθών και των συντάξεων είχε ως επακόλουθο τη μεγάλη αύξηση της φτώχειας. Τα επόμενα χρόνια μειώθηκε ο μέσος όρος ζωής των ανδρών κατά 6 χρόνια και των γυναικών κατά 3 χρόνια. Κύριες αιτίες θανάτου των πολιτών ήταν: καρδιαγγειακές παθήσεις και βίαιοι θάνατοι (αυτοκτονίες, ατυχήματα, σωματικές κακώσεις, δηλητηριάσεις). Η αυξημένη Ρωσική θνησιμότητα αποδόθηκε σε δύο, κυρίως, αιτίες: τις στρεσογόνες κοινωνικο-οικονομικές καταστάσεις και τη σοβαρή κατανάλωση οινοπνευματωδών.[3,4]

Στις χώρες της Βαλτικής (Λετονία, Εσθονία, Λιθουανία) καταγράφηκαν δραματικές κοινωνικές και οικονομικές αλλαγές την ίδια χρονική περίοδο. Η ανεξαρτητοποίηση αυτών των κρατών και ο ταχύτατος κοινωνικός μετασχηματισμός οδήγησαν στην απώλεια της στήριξης της πολιτείας προς τους πολίτες. Καταγράφηκε μια ταχύτατη αύξηση της φτώχειας, της ανεργίας, των διαζυγίων, της γενικής θνησιμότητας και ειδικότερα αύξηση των αυτοκτονιών. Οι κοινωνικές αλλαγές επηρέασαν περισσότερο τους άνδρες λόγω του παραδοσιακού τους ρόλου για τη φροντίδα-ευζωία της οικογένειας και της προσκόμισης οικονομικών πόρων.[1,3]

Στα 1997, μια οικονομική κρίση άρχισε στην Ταϊλάνδη, που γρήγορα εξαπλώθηκε στις οικονομίες των γειτονικών χωρών όπως στις Φιλιππίνες, στη Νότια Κορέα, στην Ιαπωνία, στην Ινδία, στη Μαλαισία και στην Ινδονησία. Παρατηρήθηκε μια αύξηση της γενικής θνησιμότητας και κυρίως αύξηση των αυτοκτονιών στις περισσότερες χώρες. Οι επιδημιολογικές μελέτες απέδωσαν την αυξημένη θνησιμότητα στη γρήγορη και μεγάλη αύξηση της ανερ-

γίας και στη μείωση του εισοδήματος των πολιτών. Αξίζει να τονισθεί ότι ορισμένες χώρες όπως η Σιγκαπούρη και η Ταϊβάν επηρεάστηκαν ελάχιστα από την κρίση. Το γεγονός αποδόθηκε στη μικρή επίδραση της κρίσης στο ακαθάριστο-εθνικό προϊόν της χώρας και στους χαμηλούς δείκτες ανεργίας.[3–5]

Η Ευρωπαϊκή οικονομική κρίση άρχισε το 2008 και οι επιπτώσεις της ήταν ιδιαίτερα εμφανείς στον Ελληνικό πληθυσμό.[6] Η ανεργία αυξήθηκε δραματικά, από 6,6% το 2008 σε 22% το 2012 ενώ η ανεργία των νέων έφθασε το 45%. Η Ελληνική κυβέρνηση δανείστηκε από το Διεθνές Νομισματικό Ταμείο και τα κράτη-μέλη της Ευρωπαϊκής Ένωσης, κάτω από αυστηρούς όρους που περιλάμβαναν δραστικές περικοπές των δημοσίων δαπανών. Αποτέλεσμα αυτών των δεσμεύσεων ήταν η μείωση των κλινών και των εργαζομένων στα δημόσια νοσοκομεία και γενικά, η μείωση των δαπανών υγείας. Παρά τις παραπάνω δράσεις, καταγράφηκε μια αύξηση των εισαγωγών στα δημόσια νοσοκομεία με παράλληλη μείωση των εισαγωγών στα ιδιωτικά νοσοκομεία. Ακόμα, σύμφωνα με πρόσφατα δεδομένα παρατηρήθηκε αύξηση των αυτοκτονιών και των αποπειρών αυτοκτονίας, αύξηση των βίαιων συμπεριφορών και των ανθρωποκτονιών, αύξηση των οροθετικών για HIV ατόμων και αύξηση των χρηστών ηρωίνης.[7–9]

Τι μπορούμε να μάθουμε από την εμπειρία των μεγάλων οικονομικών κρίσεων που αναφέρθηκαν; Το κύριο συμπέρασμα είναι ότι η επίδραση της κρίσης στην υγεία των πολιτών εξαρτάται, κυρίως, από το βάθος και τη διάρκεια της κρίσης και ακόμα, από την ικανότητα ανάπτυξης μηχανισμών προστασίας της κοινωνίας. Σε συνθήκες οικονομικής κρίσης, οι άνεργοι, οι φτωχοί, οι πάσχοντες από χρόνιες σωματικές ή ψυχικές παθήσεις αποτελούν τις ομάδες υψηλού κινδύνου για νοσηρότητα/θνησιμότητα και αυτοκαταστροφικές συμπεριφορές. Σε δύσκολους καιρούς οικονομικών-κοινωνικών κρίσεων ως πρώτη προτεραιότητα των χωρών θα πρέπει να είναι η προστασία των ατόμων υψηλού κινδύνου.[1,4,10]

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Βιβλιογραφία

1. Stuckler D, Basu S, Suhrcke D, Cutts A, McKee M. The health implications of financial crisis: A review of the evidence. *Ulster Med J* 2008, 78:142–145
2. Stucker D, Meissner C, Fishback P, Basu S, McKee M. Banking crises and mortality during the Great Depression: evidence from US urban populations 1929–1937. *J Epidemiol Commun Health* 2012, 66:410–419
3. Falagas ME, Vouloumanou EK, Mavros MN, Karageorgopoulos DE. Economic crises and mortality: a review of the literature. *Int J Clin Pract* 2009, 63:1128–1135
4. Uutela A. Economic crisis and mental health. *Curr Opinion Psychiatry* 2012, 23:127–130
5. Chang SS, Gunnell D, Sterne JA, Lu TH, Cheng AT. Was the economic crisis 1997–1998 responsible for rising suicide rates in East/Southeast Asia? All time trend analysis for Japan, Hong-Kong, South Korea, Taiwan, Singapore and Thailand. *Soc Sci Med* 2009, 68: 1322–1331
6. Stuckler D, Basu S, Suhrcke D, Cutts A, McKee M. Effects on the 2008 ressesion on health: a first look on European data. *Lancet* 2011, 378:124–125
7. Keltikelenis A, Katanikolos M, Papanikolas I, Basu S, McKee M, Stuckler D. Health effects of financial crisis: omens of a Greek tragedy. *Lancet* 2011, 378:1457–1458
8. Giotakos O, Tsouvelas G, Kontaxakis V. Suicide rates and mental health services in Greece. *Psychiatriki* 2012, 23:29–38
9. Triantafyllou K, Angeletopolou C. IFM and European co-workers attack public health in Greece. *Lancet* 2011, 378:1459–1460
10. Giotakos O. Financial crisis and mental health. *Psychiatriki* 2010, 21:195–204

Research Article
Ερευνητική εργασία

The development of manualised cognitive behaviour treatment for adults with mild intellectual disability and common mental disorders

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People with intellectual disability are at a greater risk of developing common mental disorders. In the United Kingdom, the National Institute for Health and Clinical Excellence guidelines recommend cognitive behavioural therapy (CBT) as the treatment of choice for such problems. Even though there is growing evidence that people with mild intellectual disability can benefit from CBT, there are no manuals to assist in the delivery of the treatment. Previously published material from journals and books describing both CBT in people with intellectual disability and the general population was reviewed to create the first draft. Further consultations with professionals and service users with intellectual disability on the content, accessibility and language that was used in the manual were carried out. Specific materials were developed for use in the therapy sessions and for homework. The manual, written for trained therapists, provides generic information about communication and thinking styles in people with mild intellectual disability and describes in detail how to conduct each session. It contains also contains the materials and a leaflet to help carers support the treatment. Manualised treatments are helpful in maintaining a consistent approach to treatment and may be more beneficial for hard to reach population groups.

Key words: Cognitive behavioural therapy, manual, intellectual disability.

Introduction

Recent studies have highlighted that people with intellectual disability* are at an increased risk of developing common mental disorders, with depression and anxiety being diagnosed most commonly.[1] Richards et al (2001)[2] and Maughan et al (1999)[3] compared adults with and without intellectual disability in a British birth cohort and found a four- to six-fold increase of common affective disorders in adults with mild intellectual disability.

The National Institute of Health and Clinical Excellence (NICE) in the United Kingdom advocates cognitive behavioural therapy (CBT) as one of the most effective forms of treatment for depression and anxiety disorders in the general population.[4,5] Current policy by the Department of Health[6] states that people with intellectual disability should have the same access to healthcare as those without intellectual disability. However, whilst CBT is extensively being used in the general population, it is not readily available to people with mild intellectual disability who often have cognitive and complex communication needs. Developing a manualised CBT guide would be the first step to ensure that such psychological interventions can be delivered to people with intellectual disability who may access not just specialist but primary and/or secondary mental health services.

Despite previous concerns about the ability of people with intellectual disability to use psychological interventions, there is now growing evidence that CBT is being offered in clinical practice and it is suitable to treat a range of mental health problems in people with intellectual disability. These include psychosis,[7] obsessive-compulsive disorder,[8] anxiety,[9,10] depression[11–13] and anger.[14,15] Prout & Nowak-Drabik[16] conducted a meta-analysis on the efficacy of psychotherapy in people with intellectual disability. They found a total of 92 studies that evaluated the effects of psychotherapy in children and adults with mild to severe intellectual disability from a variety of settings including community and residential care. They reported that 13% of the studies reviewed used cognitive/cognitive-behavioural techniques. Their findings also suggest that cognitive/cognitive-behavioural interventions appear to result in moderate degree of change as reported by the outcome measures and effectiveness in terms of benefit to people with intellectual disability. However, most CBT interventions have previously focused on observable behavioural rather than cognitive aspects of the disorders.[17,18]

Evidence of CBT in depression

A single case study in mild intellectual disability showed improvements in behavioural symptoms of depression, e.g. crying and depressed mood, following CBT.[19] Furthermore, Lindsay et al (1999)[10] found that five individuals with mild to moderate intellectual disability reported a 25% decrease in scores of depression (on the Beck Depression Inventory and Zung Depression Scale) following individual CBT intervention, the results for which were maintained at six months follow-up. McCabe et al (2006)[12] developed a 5-week group treatment programme that was designed to enhance social skills, promote participation in social activities, identify and change negative cognitions using CBT techniques. The treatment group showed significant improvement in scores of depression, positive feeling about the self and reported less negative automatic thoughts compared to a waiting list control group.[12] These positive changes were maintained at 3-month follow up. McGillivray et al (2008)[13] modified McCabe et al (2006)[12] CBT intervention and trained 13 staff members employed at two different community-based agencies to administer a 12-week group CBT program to 47 individuals with mild intellectual disability and symptoms of depression. Results showed significant improvements cognitive and behavioural aspects of depression and changes in automatic negative thoughts for the individuals who received the CBT intervention compared to a waiting list control.[13]

* Intellectual disability is defined (ICD10) as reduced IQ (<70), deficient adaptive capacity and being evident during the developmental period. In Mild intellectual disability IQ ranges from 50 to 69 and the person has sufficient verbal ability and may live independently.

Evidence of CBT in anxiety

Lindsay et al (1997)[9] used adapted CBT techniques to treat anxiety in two cases with mild intellectual disability and reported positive changes on the Beck Anxiety Inventory and improvements in anxiety related behaviour reported by staff observing the patients. These results were maintained over 18 months. The authors reported significant reduction in self-reported measures of anxiety in 15 individuals with mild/moderate intellectual disability who received an average of 23 individual CBT sessions.

Aim

Despite CBT techniques being used n clinical settings with published reports showing positive changes in symptoms of depression and anxiety, there are no specific guidelines describing how it should be carried out in individual therapy.[20] We report the process by which we developed a cognitive behavioural therapy manual for CBT therapists to administer individual therapy to people with mild intellectual disability who suffer from common mental disorders. This was the first phase of a feasibility study of the evaluation of manualised individual CBT for common mental disorders in people with mild to moderate intellectual disability.

Material and method

We undertook a literature search to find relevant information and drafted a preliminary outline of the manual. We consulted with experts regarding the content before a full draft was produced. Concurrently, we developed accessible materials suitable for people with intellectual disability, which were piloted in a service user consultation group. The developmental process was led by the research team comprising of specialists in the field of intellectual disability, CBT and health interventions (psychiatry, psychology, speech and language therapy, research methodology). An accessible information worker with several years of experience in developing accessible information for people with intellectual disability acted as an advisor to the project.

Literature search

We conducted a literature search using MEDLINE, PsycINFO, PUBMED and EMBASE, in addition to specialist journals including Journal of Applied Research in Intellectual Disability (JARID), Journal of Intellectual Disability Research (JIDR) and the American Journal on Intellectual and Developmental Disability (AJIDD) using the following keywords: "cognitive behav* therap*", "CBT", "learning disabilit*" "intellectual disabilit*", "mental retardation", "depression" and "anxiety". Relevant books and book chapters describing cognitive behaviour interventions in the general population (i.e. children, adolescents and adults) and in people with intellectual disability were hand searched for information and materials. CBT materials for homework tasks were mainly adapted from the following sources: Think Good Feel Good,[21] Wilson and Branch,[22] Alex Kelly[23] and Gulbenkoglu & Hagiliassis.[24]

Suitability for treatment

Several studies have found that people with intellectual disability have the prerequisite skills to understand the concepts of CBT and in order to engage in this form of therapy.[24–26] These include the ability to link situations to emotions,[24] to correctly identify emotions[25] and to have the capacity to differentiate between thoughts, feelings and behaviour.[26] Sams et al[26] found that the identification of behaviours and feelings is linked to verbal ability and thoughts with general IQ. Thoughts, feelings, and behaviours are therefore more likely to be understood and correctly identified by people with higher verbal ability and IQ. People with mild intellectual disability perform better when linking situations to emotions, rather than links involving beliefs, but many may require some training in cognitive mediation before CBT treatment.[24]

The individual's level of comprehension, level of expression, their ability to self-report and self-regulation skills are all important factors in assessing suitability for CBT in people with intellectual disability.[27] Knowledge acquisition requires skills such as controlling attention, and effective memory function.[28] People with intellectual disability may have impairments in both of these domains which may affect concentration span, ability to screen out extraneous information and to attend to relevant stimuli.[28,29] Thus, the therapist needs to control the pace of the session, for example, slowing down to reduce the amount of information the

individual is required to process and repeating information to support retention. The use of visual aids such as pictorial representations, drawings and signs (e.g. Makaton, Walker & Armfield[30]) for certain tasks such as mood monitoring, thought-feeling diaries, presenting temporal concepts and identifying automatic negative thoughts would help facilitate understanding and processing of relevant information.[31] Other modifications include the use of repetition and encouraging "overlearning" in some scenarios, along with a need for flexibility in the number and length of the sessions offered.[20] Previously modified CBT interventions in people with intellectual disability for the treatment of anger have highlighted sections on psycho-education as essential.[32]

How to manage homework tasks

Evidence from research in the general population indicates that homework compliance in CBT is associated with improvements in treatment outcomes.[33] This provides the individual with an opportunity to practice new skills and incorporate them into his/her daily routine. Rose et al (2005)[34] found that in group CBT for anger, service users who were accompanied by a member of care staff (either from their residential home, place of work or from a community support team) made better progress in the therapy. By having a carer/support worker in the session helped to provide greater continuity between sessions and staff members were more able to assist the participants in practicing skills outside the session.[35] Compliance with homework tasks depends on a number of factors such as therapist and/or clients' attitudes towards the tasks and task characteristics (such as the difficulty of the task and the length of the task), these factors are further discussed elsewhere.[36]

Developing accessible materials (service user workbook)

We developed the service user accessible materials using easy read guidelines that are based on "Make it clear" guidelines on accessible information by MENCAP,[37] a leading UK wide charity for people with intellectual disability and their carers. The two main components of delivering accessible information are to use simpler language and pictures to support the written message. The language needs to be jargon-free and if a difficult word or concept must be used (i.e. "core beliefs") it should be accompanied by a simple definition. Sentences should be as short as possible. Other guidance suggests that there should be one or two ideas expressed per sentence.[37] Other tips of accessible information can be found in table 1.

In our manual we use pictures from the Photosymbols Version 3 (www.photosymbols.com) which is the preferred way of developing accessible information for people with intellectual disability and is the primary symbol resource for many organisations that produce easy read information. The Photosymbols collection contains 3000 pictures and many of their models are people with intellectual disability themselves. These images are easier to recognise and understand because they are photorealistic and in colour. They work well as symbols because they have been cut out to remove the extraneous detail often found in photographs. The text and supporting images should be seen as a starting point in the communication of the information in the workbook. Talking around the information, giving different examples and checking back for evidence of understanding should all be part of the therapist's approach.

Consultations

Consultation with experts

Once a draft of the therapist's manual was completed components were consulted upon in a two hour session with 17 participants (10 consultants and seven senior trainee psychiatrists) who have had several years of clinical experience in working with

Table 1. Tips on accessible information.

- Text in an easy to read Sans Serif font (e.g. Arial)
- Main body of the text should be size 16 point or higher
- Document should be laid out so that the pictures are on the left side of the page and the text on the right; it allows the service user information to be placed first as the English language is read from left to right
- Use bullet points for lists
- Text should be laid out so that there is white space between the sentences and the text is not densely together (this usually occurs naturally when pictures are inserted into the document)

this client group. The participants discussed the content of the draft manual sections and provided comments and other amendments for sections. Details of the feedback received are shown in table 2. We also asked the CBT course tutor of an English University that provides CBT training to professionals working in intellectual disability to comment on the manual contents and layout.

Consultation with service users

The worksheets and homework materials were taken to a service user consultation group that has previously helped with producing several service related accessible materials over a five year period. The group members represent a range of people with intellectual disability and levels of communication. They have previously worked on many of the Camden Intellectual Disability Service publications such as brochures, leaflets, the intellectual disability pages of the Local Authority website, complaint forms, posters and subtitles for audio/visual materials developed for the wider service users group.

The two consultation sessions with the service users focused on the use of language, the use/appropriateness of photosymbols, the layout of the documents and the content of the information, to check that adaptations and modifications to the CBT materials were suitable and could be understood. We discussed the materials to ensure that abstract concepts were successfully presented in a tangible manner. Each consultation consisted of seven participants with mild- moderate intellectual disability. The group was first briefed on the purpose of the consultation by KA using guidelines to accessible information to structure the discussion and facilitated by RL (accessible information worker). Five worksheets including the cognitive model, the body map of symptoms of anxiety, the concept of "future" in relation to the cognitive triad, the concept of core beliefs and the assertiveness scale were selected for consultation. Participant feedback indicated that the information in the documents was understood when text was read out and explained with further examples. Further details are shown in table 3.

Table 2. Expert consultation feedback.

- Inclusion of visual aids
- Inclusion of list about therapist skills
- Describe session duration and content
- Describe possible outcomes

Results

The manual describes a step by step approach to CBT for depression and anxiety in people with mild to moderate intellectual disability. It is divided into two separate parts.

Part 1 provides a review of depression, anxiety, the cognitive behavioural approach to therapy, and the

Table 3. Service user consultation feedback.

- The CBT model: the participants were consulted on the adapted CBT model illustration developed for with people with intellectual disability in the project. The participants understood that thoughts, feeling and behaviour were linked when the model talked through with lots of examples
- Body map of symptom of anxiety: The group went through the symptoms one-by-one and were asked if they understood the symptoms. For abstract symptoms such as "butterflies in the stomach", the group was asked to describe it in their own words. The term was understood and alternative words used where, "funny feeling inside the tummy" and "feeling nervous". The group also raised concerns that even though they understood the symptom "tingling feeling in your fingers and toes" they knew others who might not understand it
- The concept of future (the cognitive triad): It was agreed in the group that people would generally find it difficult to understand the term "future". The group decided on an alternative term which was "ahead" or "doing new things"
- The concept of core beliefs: One of the principles of accessible information is that if a substitute word is not found, the term needs to be explained. Since the idea of "core beliefs" in very important in CBT, it would be important to teach/familiarise the client with the term. Therefore, it was important to see if the explanation was accessible. The service users were able to easily grasp the concept and understand the term core beliefs with examples
- Assertiveness scale: The terms (assertive, aggressive and passive), the definitions and the layout of the continuous scale were consulted upon, and agreed to use in the manual

therapeutic relationship in the context of intellectual disability. The latter half of this section focuses on communication and explains how the therapist can modify their communication in a therapeutic setting to more effectively address the needs of the clients. Furthermore, to assess the service user's communication and cognitive skills, we have decided to include a language assessment that the therapist is required to administer in the initial sessions to gauge the service user's strengths and verbal limitations, in order to aid appropriate engagement in the treatment. The Test for Receptive Grammar (TROG-2; Bishop[38]) is a receptive language test that is commonly used by Speech and Language Therapists, in assessing understanding of receptive grammar and helps tease apart possible reasons for failing to understand what is said.

Part 2 describes in detail the process of therapy over 18 sessions; the first five sessions are about the introduction of the service user to the treatment and the assessment of his/her level of communication and cognitive level. The intermediate phase comprises sessions six to 15 and the final phase sessions 16–18. The manual focuses on cognitive aspects of treatment such as thinking style errors, the cognitive triad, core beliefs and linking thoughts, feelings and behaviours (i.e. using the ABC form in an accessible format). We have also included a chapter on psychoeducation with accessible information on symptoms of depression and anxiety and exercises that can help the service user recognise his/her symptoms effectively. All materials are included on a CD within the manual so they can be reproduced as needed.

Discussion

The manual is designed for therapists who have CBT training, but have little to no experience in working with clients who have intellectual disability. It outlines a therapeutic protocol that can be applied in treatment. The accessible work/homework sheets are incorporated into the manual along with an outline on how they could be used during the sessions. The work/homework sheets are designed as stand alone tasks to provide even greater flexibility in how they can be used.

Homework and carer support

McVilly et al (1997)[39] reported that it is useful to provide educational support and additional information for the carer to improve his/her ability to provide support in therapy. Availability of a carer/support worker is an integral part of the treatment to help the service user with homework tasks, promote adherence to treatment and prepare for the sessions. Where necessary the carer/support worker should also be involved in the sessions to offer encouragement and motivation. We also see the involvement of the carer/support worker as essential for the service users to move successfully through the treatment programme. However, Willner (2006)[40] argued that the therapist also needs to be aware of the support worker's level of engagement and motivation in addition to that of the service user's.

Advantages and limitations of manualised interventions

As CBT in intellectual disability is relatively new in clinical practice and research, manuals can be advantageous and helpful as they allow for consistency in the delivery of the intervention, facilitate training professionals in specific clinical techniques and strategies and assist therapist supervision.[41] Wilson (1998)[42] argued that treatment manuals encourage a pragmatic approach to therapy without hindering clinical practice. A manualised treatment does not supersede clinical judgment but allows a consistent evidence based perspective which may be more likely to have a successful outcome.

Implications for research and clinical practice

This is still a developing area in research and clinical settings and a manual would be a valuable tool for training professionals in the therapeutic skills required to work with this population group. This manual has been developed for accredited CBT therapists; however the manualised treatment program requires further evaluation if it is to be used by other health professionals or frontline staff who have a regular contact with the service users but may not have received training in CBT.

Η ανάπτυξη εγχειριδίου γνωσιακής-συμπεριφορικής θεραπείας για ενηλίκους με ήπια νοητική υστέρηση και ψυχικές διαταραχές

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Άτομα με νοητική αναπηρία ευρίσκονται σε μεγαλύτερο κίνδυνο να αναπτύξουν κοινές ψυχικές διαταραχές, όπως κατάθλιψη ή άγχος. Στο Ηνωμένο Βασίλειο, το Εθνικό Ινστιτούτο Υγείας και η Κλινική Αριστείας συνιστά γνωσιακή-συμπεριφεριολογική θεραπεία (CBT) ως τη θεραπεία επιλογής για αυτές τις παθήσεις. Η υπάρχουσα βιβλιογραφία και η Κλινική εμπειρία δείχνουν ότι η CBT χρησιμοποιείται αρκετά σε υπηρεσίες για άτομα με νοητική υστέρηση παρόλο που δεν υπάρχει ικανοποιητική ερευνητική βάση όσον αφορά στα θετικά αποτελέσματα της μεθόδου. Επίσης δεν υπήρξε μέχρις πρόσφατα εγχειρίδιο που να περιγράφει με λεπτομέρεια την εφαρμογή της σε Κλινικό περιβάλλον. Στο άρθρο περιγράφουμε το πρώτο στάδιο μιας ερευνητικής μελέτης που μας επέτρεψε να αναπτύξουμε το θεραπευτικό εγχειρίδιο. Δημοσιευμένο υλικό από περιοδικά και βιβλία που περιγράφει τόσο CBT σε άτομα με ήπια νοητική υστέρηση όσο και στον γενικό πληθυσμό επανεξετάστηκε για τη δημιουργία του πρώτου σχεδίου. Δύο περαιτέρω διαβουλεύσεις πραγματοποιήθηκαν με: (α) Ψυχιάτρους, ψυχολόγους και άλλους ειδικούς στη νοητική υστέρηση και (β) με τους χρήστες υπηρεσιών για νοητική υστέρηση ώστε να ελέγξουμε αν το περιεχόμενο, η προσβασιμότητα και η γλώσσα που χρησιμοποιήθηκε στο εγχειρίδιο ήταν κατάλληλα. Συγκεκριμένα υλικά που στηρίζονται σε εικόνες και απλοποιημένο λόγο αναπτύχθηκαν για χρήση στη διάρκεια της θεραπείας και για ασκήσεις στο σπίτι ή σε άλλους χώρους. Το εγχειρίδιο, γραμμένο για εκπαιδευμένους θεραπευτές περιέχει κεφάλαια τα οποία περιέχουν γενικές πληροφορίες σχετικά με τον τρόπο επικοινωνίας και σκέψης των ατόμων με ήπια νοητική υστέρηση και περιγράφουν λεπτομερώς τον τρόπο με τον οποίο ο θεραπευτής διαχειρίζεται τη συνεδρία. Περιέχει επίσης ένα CD με τα υλικά και το φυλλάδιο για τους υποστηρικτές ή τα μέλη της οικογένειας ώστε να βοηθήσουν το άτομο στη θεραπεία. Ατομική CBT που στηρίζεται σε εγχειρίδιο βοηθά στη διατήρηση της ποιότητας και τη συνεπή προσέγγιση της θεραπείας σε διάφορα περιβάλλοντα. Παράλληλα, προσφέρεται στο να έχουν καλύτερη εμπειρία αυτής της αντιμετώπισης ειδικοί πληθυσμοί που συνήθως έχουν δυσκολία στην πρόσβαση υπηρεσιών ψυχικής υγείας.

Λέξεις ευρετηρίου: Γνωσιακή-συμπεριφορική θεραπεία, εγχειρίδιο, νοητική υστέρηση

References

1. Azam K, Sinai A, Hassiotis A. Mental ill-health in adults with learning disability. *Psychiatry* 2009, 8:376–381
2. Richards M, Maughan B, Hardy R, Hall I, Strydom A, Wadsworth M. Long-term affective disorder in people with mild learning disability. *Br J Psychiatry* 2001, 179:523–527
3. Maughan B, Collishaw S, Pickles A. Mild mental retardation: psychosocial functioning in adulthood. *Psychologic Med* 1999, 29:351–366
4. National Institute for Health and Clinical Excellence. Depression: The treatment and management of depression in adults: CG 90.

London, National Institute for Health and Clinical Excellence, 2009

5. National Institute for Health and Clinical Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care:CG 113. London, National Institute for Health and Clinical Excellence, 2011
6. Department of Health. Valuing people: a new strategy for learning disability for the 21st century. Department of Health Cmd 5806 (London, DoH), 2001
7. Kirkland J. Cognitive-behaviour formulation for three men with learning disability who experience psychosis: how do we make it make sense? *Br J Learn Disabil* 2005, 33:160–165
8. Willner P, Goody R. Interaction of Cognitive Distortions and Cognitive Deficits in the Formulation and Treatment of Obsessive-Compulsive Behaviours in a Woman with an Intellectual Disability. *J Appl Res Intell Disabil* 2006, 19:67–73
9. Lindsay WR, Neilson C, Lawrenson H. Cognitive-behaviour therapy for anxiety in people with learning disability. In: Stenfert B, Kroese B, Dagnan D, Loumidis K (eds) *Cognitive-Behaviour Therapy for People with Learning Disability*. Routledge, London, 1997:124–140
10. Lindsay WR. Cognitive therapy. *Psychologist* 1999, 12:238–241
11. Lindsay WR, Howells L, Pitcaithly D. Cognitive therapy for depression with individuals with intellectual disability. *Br J Medic Psychol* 1993, 66:135–141
12. McCabe M, McGillivray J, Newton D. Effectiveness of treatment programmes for depression among adults with mild/moderate intellectual disability. *J Intellect Disabil Res* 2006, 50:239–247
13. McGillivray J, McCabe M, Kershaw M. Depression in people with intellectual disability: An evaluation of a staff-administered treatment program. *Res Developmen Disabil* 2008, 29:524-536
14. Rose J, West C, Clifford D. Group intervention for anger in people with intellectual disability. *Res Development Disabil* 2000, 21:171–181
15. Gulbenkoglu H, Hagiliassis N. Anger Management:An Anger Management training Package for Individuals with Disability. Jessica Kingsley Publishers, London, 2006
16. Prout T, Nowak-Drabik K. Psychotherapy With Persons Who Have Mental Retardation: An Evaluation of Effectiveness. *Amer J Mental Retardation* 2003, 108:82–93
17. Willner P. The effectiveness of psychotherapeutic interventions for people with learning disability: a critical overview. *J Intellect Disability Resear* 2005, 49:73–85
18. Alford JD, Locke BJ. Clinical responses to psychopathology of mentally retarded persons. *Am J Mental Deficien* 1984, 89:195–197
19. Dagnan D, Chadwick P. Cognitive behaviour therapy for learning disability. In: Stenfert-Kroese B, Dagnan D, Loumidis K (eds) *Cognitive behaviour therapy for people with learning disability*. Routledge, London, 1997:114–127
20. Haddock K, Jones R. Practitioner consensus in the use of cognitive behavioural therapy for individuals with learning disability. *J Intellect Disabil* 2006, 10:221–230
21. Stallard P. *Think Good, Feel Good*. John Wiley & Sons Ltd, Chichester, 2002
22. Wilson R, Branch R. *Cognitive Behavioural Therapy for Dummies*. John Wiley & Sons Ltd, Chichester, 2006
23. Kelly A. *Adults with a Learning Disability*. Winslow Press Ltd, Oxon, 2000
24. Dagnan D, Chadwick P, Proudlove J. Towards an Assessment of suitability of people with Mental Retardation for Cognitive Therapy. *Cognit Therapy Research* 2000, 24:627–636
25. Joyce T, Globe A, Moody C. Assessment of the Component Skills for Cognitive Therapy in Adults with Intellectual Disability. *J Appl Res Intellect Disabil* 2006, 19:17–23
26. Sams S, Collins S, Reynolds S. Cognitive therapy abilities in people with learning disability. *J Appl Res Intellect Disabil* 2006, 19:25–33
27. Kroese S, Dagnan D, Loumidis K. *Cognitive-Behaviour Therapy for People with Learning Disability*. Routledge, London, 1997.
28. Baroff GS, Olley JG. *Mental Retardation. Nature, cause and management*. 3rd edition. Bruner-Mazel, New York, 1999
29. Sturmey, P. Cognitive therapy with people with intellectual disability:a selective review and critique. *Clin Psychol Psychother* 2004, 11:222–232
30. Walker M, Armfield IA. *What is the Makaton Vocabulary*? Special Education: Forward Trends 1987, 8:19–20
31. Brown M, Marshall K. Cognitive behaviour therapy and people with learning disability: implications for developing nursing practice. *J Psych Ment Hlth Nurs* 2006, 13:234–241
32. Willner P, Tomlinson, P. Generalization of Anger-Coping Skills from Day-Service to Residential Settings. *J Appl Res Intellect Disabil* 2007, 20:553–562
33. Kazantzis N, Deane F, Ronan K. Homework Assignments in Cognitive and Behavioral Therapy:A Meta-Analysis. *Clin Psychol Sci Pract* 2000, 7:189–202
34. Rose J, Loftus R, Flint B, Carey L. Factors associated with the efficacy of group intervention for anger in people with intellectual disability. *Br J Clin Psychol* 2005, 44:305–317
35. Kazantzis N, Anderson G. Social problem-solving skills training for adults with mild intellectual disability: A multiple case study. *Behav Change* 2008, 25:97–108
36. Kazantzis N, Deane F, Ronan K. Assessing Compliance with Homework Assignments:Review and Recommendations for Clinical Practice. *J Clin Psychol* 2004, 60:627–641
37. Mencap. *Make it Clear*, 2008. (Cited 03 June 2010) Available from:www.mencap.org.uk
38. Bishop DVM. The *Test for Reception of Grammar*, version 2 (TROG-2). Psychological Corporation, London, 2003
39. McVilly K. Residential staff: how they view their training and professional support. *Br J Learn Disabil* 1997, 25:18–25
40. Willner P. Readiness for Cognitive Therapy in People with Intellectual Disability. *J Appl Res Intellect Disabil* 2006, 19:5–16
41. Wilson G. Manual-Based Treatment and Clinical Practice. *Clin Psychol Sci Pract* 1998, 5:363–375
42. Wilson G. Manual-based treatments:The clinical application of research findings. *Behav Res Ther* 1996, 34:295–314

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Research Article
Ερευνητική εργασία

Cortical thickness and oscillatory phase resetting: A proposed mechanism of salience network dysfunction in schizophrenia

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Schizophrenia is characterised by both electrophysiological abnormalities and consistent changes in the structure of cortical grey matter. But the relationship between these two observations is largely unknown. Structural changes reported in schizophrenia include reduced grey matter volume, thickness and surface area in several cortical regions, but most frequently in the insula and anterior cingulate cortex. These two regions together constitute an intrinsic brain circuit known as the "Salience Network", which has a key role in stimulus processing. During stimulus processing tasks, evoked activity is noted using electroencephalography (EEG). Phase resetting of ongoing oscillations contributes to this evoked activity. Neuronal oscillations play a crucial role in cerebral recruitment during cognitive tasks, and influencing the oscillatory phase can modulate cortical excitability and the transition between various cognitive states. At a network level, such a transition or switch is thought to be enabled by the Salience Network. In this study, we investigated the relationship between the cortical thickness in the Salience Network (measured using MRI) and the degree of phase resetting observed during an oddball task (measured using EEG) in 18 medicated male patients in a clinically stable phase of schizophrenia and 20 age and gender matched healthy controls. We obtained a measure of partial phase resetting after a stimulus is presented, and a second measure representing mean evoked activity, using the methods proposed by Martinez-Montes. Using MRI analysis, we have firstly shown that there is a significant loss of cortical thickness of regions that constitute the Salience Network in patients with schizophrenia. EEG analysis revealed that in healthy controls, the expected relationship between phase resetting and evoked electrical activity is observed, but in patients with schizophrenia the theta phase resetting is a weak predictor of the activity evoked by attending to a target stimulus, though the difference between the groups did not reach statistical significance in the present sample. Furthermore, in patients with schizophrenia the reduced thickness in the Salience Network is associated with the inefficient phase resetting of theta oscillations. Our findings suggest that the grey matter reduction seen in the Salience Network in patients with schizophrenia has substantial functional consequences. In particular, the structural defect of the insula that is seen in schizophrenia is likely to be associated with less efficient recruitment of brain circuits for processing information. This implies a possible mechanism by which disruptions in the intrinsic Salience Network can result in a general disturbance in salience detection seen in schizophrenia.

Key words: Salience network, phase resetting, oscillations, insula, cingulate.

Introduction

Voxel based morphometry (VBM) in chronic schizophrenia consistently shows significant reduction in the grey matter volume in the insula and the anterior cingulate cortex.[1,2] Structural changes in these two regions are thought to be important in the pathophysiology of schizophrenia.[3] In particular, insula shows significant grey matter reduction in patients with at risk mental state who later develop schizophrenia-like illness,[4,5] and thus predicts transition from prodrome to established psychosis.[6] The mechanism by which such a consistent grey matter loss across the insula and ACC influences the clinical and neuropsychological features of schizophrenia remains unknown.

Anterior insula and anterior cingulate constitute a "Salience Network", one of the three major intrinsic connectivity networks (ICN) identified using functional connectivity analysis in healthy individuals.[7] Along with other ICNs (Central Executive Network (CEN) comprised of dorsolateral prefrontal cortex and the intraparietal sulcus and Default Mode Network (DMN) comprised of medial prefrontal cortex and posterior cingulate cortex), the Salience Network (SN) is involved in attentional modulation and information processing.[7] The DMN includes a set of regions related to a "resting" mode of introspective mental activity.[8,9] These regions characteristically show reduced neural activity when attending to tasks. In contrast, during task performance, both the SN and the CEN are activated.[10] The SN is thought to act as a system equipped to identify the most homeostatically relevant material from a myriad of internal and external stimuli occurring in multiple modalities. Thus the SN sets up the executive network to operate or not on identified stimuli. Using latency analysis for Blood Oxygen Level Dependent (BOLD) activation patterns Sridharan et al[11] demonstrated temporal precedence of insular activation during event transitions and in resting state. Further, Granger causality analysis from the above study suggests that insular activation causes BOLD activations across the nodes in the executive network and deactivations across the nodes in the default mode network.

Clinical and experimental evidence strongly suggest attentional and information processing deficits in schizophrenia. Attention to both behaviorally relevant targets and infrequent and/or novel but distracting non-targets are affected in schizophrenia.[12,13] Higher distractibility from non-targets has been noted[14] in addition to higher degree of errors induced by non- relevant cues during target detection.[15] This pattern of attentional deficits is highly suggestive of a failure in both effective reorientation to relevant stimuli (i.e. salience detection) and executive control of evaluating the identified stimuli.[16,17]

Electrophysiological investigations have contributed significantly to our understanding of stimulus processing and attention system. In particular, oscillatory activity of brain has been shown to have major role in the cognitive processes related to attention, working memory and sensory perception, although the relative contributions of background oscillations and additive electrical activity in event related potentials remains a subject of debate.[18] In addition to amplitude and spectral power, much information is contained in the phase of oscillations.[19,20] Phase of ongoing oscillations at the time of stimulus presentation potentially influences the identification of a near-threshold stimulus.[21] Degree of phase locking of various frequency bands at frontal, parietal and somatosensory areas could differentiate the consciously attended stimuli from unperceived stimuli in different sensory modalities.[22,23] Thus a mechanism that sets or resets the phase of ongoing neuronal oscillations can influence attentional salience by modulating the excitability across cortical regions. In particular, phase resetting of ongoing theta oscillations has been shown to influence attention irrespective of the modality of stimulus presentation.[24]

In schizophrenia, deficits in phase resetting have been recently demonstrated.[25] Using an auditory paired-click paradigm, Brockhaus-Dumke et al[25] showed that phase resetting in lower frequency bands is significantly reduced in schizophrenia, and this effect is noted across a broad time-window before and after stimulus presentation. Abnormalities in mean amplitudes of low-frequency oscillations that are time-locked to a stimulus have been well-documented.[26] In particular, the theta oscillations that occur 200 ms to 500 ms after a task-relevant stimulus are reduced.[27] We recently reported evidence that part of the reduction in the evoked low

frequency oscillations can be explained by deficits in the phase resetting seen in schizophrenia.[28]

In summary, functional connectivity studies implicate insula and the SN in enabling the switch between task-positive and task-negative networks. On the other hand, electrophysiological studies implicate the mechanism of phase resetting of theta oscillations in this switching process that reorients the focus of attention. In schizophrenia, where abnormalities have been reported both in the SN and in phase resetting, we hypothesised a relationship between anatomical deficits in the SN and the defects in phase resetting of ongoing theta oscillations when attending to a stimulus.

Material and method

Participants

Twenty male healthy controls and 19 male patients with schizophrenia were recruited for this study. Regional Ethics Committee (Nottinghamshire) approved the study and all participants provided informed consent. The diagnosis of schizophrenia was made in accordance with Diagnostic and Statistical Manual of Mental Disorders-IV criteria[29] in a clinical consensus meeting on the basis of information provided by referring clinicians, review of existing case files and a research clinical interview performed by a trained research psychiatrist. All patients were in a state of clinical stability (defined as no more than 10 points change in Global Assessment of Functioning scale in the 6 weeks preceding the scan). Subjects with neurological disorders, current substance dependence, learning disabilities (IQ<70 using Quick Test[30]), and diagnosis of any other axis I disorder were excluded. Signs and Symptoms of Psychotic Illness interview (SSPI) was administered to quantify clinical symptoms by a trained clinician within the same week as EEG and MRI recordings.[31] All patients were receiving treatment with atypical antipsychotic medications. The healthy control group comprised twenty men free of current axis 1 psychiatric disorder, and either personal or family history of psychotic disorder, matched group-wise in age and socio-economic status (measured using National Socio-Economic Classification, NSSEC[32]) to the patient group. Controls had similar exclusion criteria to patients. Handedness was ascertained according to the Annett criteria.[33] EEG was carried out immediately prior to the MRI acquisition on the same day for all subjects.

EEG data acquisition

The EEG experiment included presentation of series of 1000Hz tones (85%) randomly intermingled with higher pitched 1500 Hz target ones (15%) at 80 dB level. Subjects made a button press response to the high-pitched target tones. Each stimulus was of 50 ms duration and 295 stimuli were presented with a fixed inter stimulus interval of 2s. Subjects undertook a practice session with 30 stimuli prior to the experiment. Scalp potentials were recorded from 128 electrodes (Biosemi, Amsterdam, The Netherlands) spread over the scalp according to the International Five Percent Electrode System for high resolution EEG[34] with a sampling rate of 256 Hz. Eye movements and blinks were recorded from electrodes lateral to each eye and an electrode placed below the right eye and another above it.

EEG data preprocessing

Processing of EEG data was carried out using Vision Analyzer 1.05 (Brain-Products, Munich, Germany). All electrodes were re-referenced to the averaged electrical potential of two electrodes on the mastoids. In order to eliminate slow drifts and high frequency noise, EEG data were band-pass filtered 0.5–50 Hz using phase-shift-free Butterworth filters with a 48 dB/octave slope. The data were corrected for eye blink artefacts according to Gratton et al[35] and stimulus-locked segments were extracted for correctly hit target trials. Large segments (1000 ms before and after stimulus) were created in order to allow for the time-frequency analysis. Artefact rejection was performed to eliminate trials contaminated by non-blink artefacts such as excessive muscular activity. Specifically, trials with a voltage greater than 100 μV were rejected automatically. The number of trials remaining after the artefact rejection did not differ between the two groups: targets-controls=45.24 (S.D. 8.52), targets-patients=44.98 (S.D. 7.22).

EEG data analysis

Analysis of EEG data to obtain measures of phase resetting and mean evoked (time-locked) activity in the theta band was carried out using the methods

proposed by Martinez-Montes et al[36] We initially extracted a representation of the time varying signal in the mid-theta range using a complex Morlet wavelet transformation of the segmented data around the centre frequency 6 Hz and with a Gaussian frequency spread of 2 Hz half-width, for the target trials. The choice of the centre frequency was based on our previous analysis.[28] We obtained T-phase, representing partial phase resetting after a stimulus is presented, and T-mean, representing mean evoked activity. In contrast to the commonly measured Inter-Trial Coherence, T-phase is a measure of phase resetting that is not confounded by a post-stimulus increase in mean amplitude (see Martinez-Montes[36] and Doege et al[28]). T-phase and T-mean are measures that quantify the relative change in phase and mean amplitude from a pre- to a post stimulus period. For both measures, the pre-stimulus period was defined as 200 ms to 600 ms before the target presentation, and post-stimulus period was defined as 0 ms to 600 ms after the stimulus presentation. The final T values are the the mean (across the post stimulus period) of the ratio measures for each post-stimulus sample derived according to the original work reported by Martinez-Montes.[36] The principle behind these measurements is illustrated in figure 1.

MRI data acquisition

Magnetic resonance scans were collected using a Philips 3-T imaging system equipped with 8-channel phased array head coil. The scanning protocol included a single high-resolution three-dimensional T1-weighted MPRAGE volume of isotropic voxel size 1×1×1 mm^3, flip angle 8°, field of view 256×256×160 mm^3.

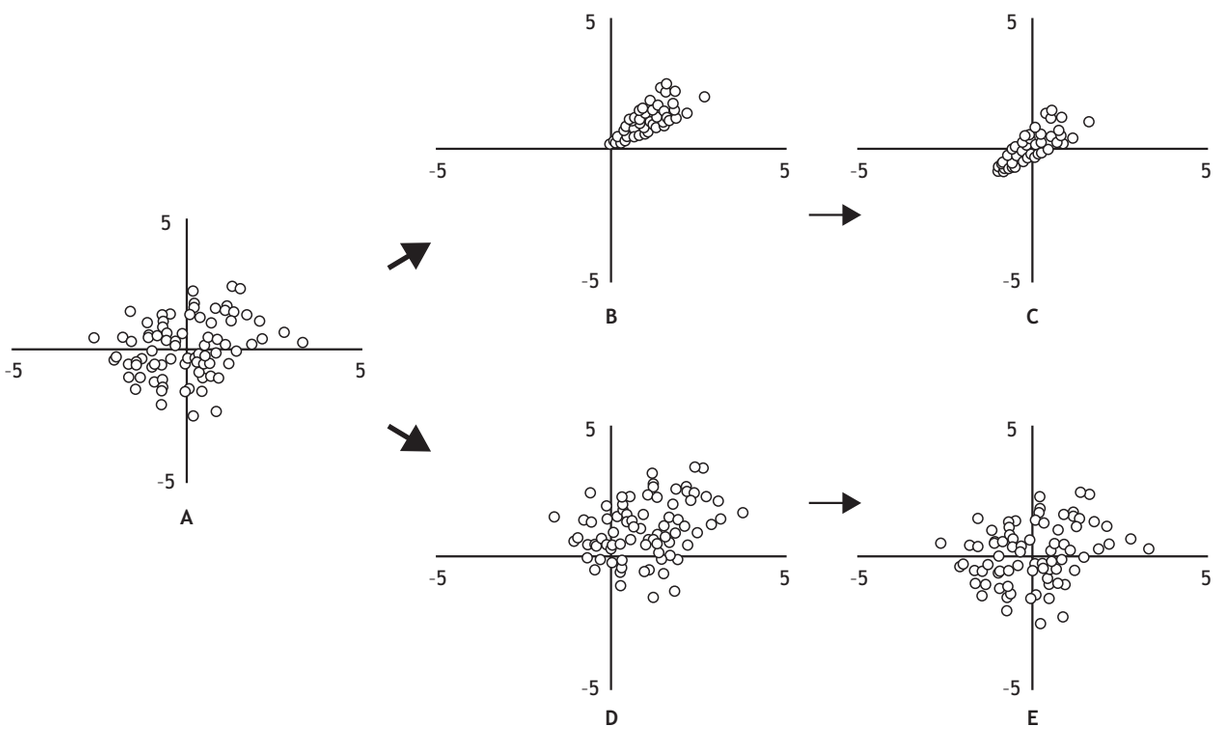

Figure 1. Plots of simulated real and imaginary components of the transformed complex wavelet coefficients. Each dot represents wavelet amplitude and phase at a specific time point, in the complex plane. Plot A represents pre-stimulus period where phases are random with zero mean. Plot B represents a partial phase resetting effect whereby the stimulus results in an alignment of previously random phases into a specified range (45˚±15˚). But when such phase resetting takes place, the amplitude of the mean signal also increases. Plot C shows phase resetting effect after subtraction of the mean signal. Plot D and E represent hypothetical post-stimulus increase in mean without a direct phase resetting effect. Plot D shows that the simple addition of a constant signal to every trial produces a phase clustering effect. Plot E shows that after subtraction of the added signal, the phases are once again randomly distributed.

MRI Image analysis

The T1 weighted images were passed through a series of image processing steps in accordance with the surface based algorithm of Freesurfer image analysis suite.[37] Automated parcellations based on Destrieux Atlas that makes use of individual sulcogyral patterns[38] were obtained. The anatomical definition of anterior cingulate follows the description given by Vogt et al[39] The anatomical definitions of the insular subregions are as follows: The circular sulcus that encircles and forms the outer boundary of the insula is divided into 3 segments: superior segment horizontally limits the insula from the subcentral and inferior frontal gyri, anterior segment vertically limits the insula from the orbital gyri, and inferior segment obliquely limits the insula from the superior aspect of the superior temporal gyrus. The central sulcus of the insula runs antero-inferiorly from the superior segment of the circular sulcus of insula. It divides the insula in two parts: the anterior short insular gyrus and the posterior long insular gyrus. The grey matter of the central sulcus itself is included with the long insular gyrus. Average thickness values across the vertices within the three anteriorly located subregions (anterior insula, anterior and superior segments of the circular sulcus), and the single anterior cingulate segment were obtained from each of the two hemispheres.

Statistical analysis

We hypothesized that: (i) Patients with schizophrenia will have reduced cortical thickness in the Salience Network (ii) Phase resetting of frontal theta oscillations will predict the evoked signal generated during target detection across the two groups. This relationship will be stronger in controls than in patients. (iii) In patients, the reduced grey matter thickness of the Salience Network will be related to frontal theta phase resetting.

To test these hypotheses, we firstly extracted cortical thickness measures across 4 parcellations for each hemisphere-3 subregions of insula and the anterior cingulate as described above. The SN thickness was analyzed using repeated measures analysis of covariance (ANCOVA) with age and global thickness as covariates, diagnosis (schizophrenia and healthy controls) as between-subject factor, and hemisphere (left and right) and regions (4 SN regions) as within-subject variables. Regional comparisons were carried out using independent t-tests for mean thickness (adjusted for age and global thickness) for each of the 4 parcellations in right and left hemisphere. To test the second hypothesis, a simple linear regression model with T-mean as dependent variable and T-phase as independent variable was constructed in patients and controls separately. A general linear model describing cortical thickness was constructed in the patient sample with hemispheric laterality (right and left) and regions (4 SN regions) as the within-subject factors while theta phase measure was entered as the major covariate of interest. Age and global cortical thickness were entered as other covariates in this model. Although our hypothesis addresses the relationship between theta phase and cortical thickness in patients, we also tested the same linear model in healthy controls to obtain an indication of whether or not the hypothesized relationship applies only to the pathological variation in thickness occurring in patients.

Results

Demographic and clinical characteristics are shown in table 1. There was no significant difference between the two groups in terms of age, parental socio-economic status and handedness index. All subjects except one patient were predominantly right handed. Patients had significantly slower reaction times than controls (controls: mean (SD) in milliseconds=352 (45), patients: mean (SD) in milliseconds=402 (72), t (1,36)=2.6, p=0.013). The intra-individual standard deviation of reaction times (ISDRT) was significantly greater in the patient group (controls: mean (SD) in milliseconds=64 (18), patients: mean (SD) in milliseconds=94 (21), t (1,36)=−4.5, p<0.001). Patients did not differ significantly from controls in the percentage of correctly hit target tones (controls=99.35% correct hits, patients=97.62% correct hits, t (1,36)=1.2, p=0.24).

SN thickness-schizophrenia vs. controls

Repeated measures ANCOVA revealed significant main effect of diagnosis [F(1,34)=9.83, p=0.004, ES=0.22] and of global thickness on SN thickness [F(1,34)=19.862, p=0.002, ES=0.37]. Age showed

a trend to be a significant covariate in the model [F(1,34)=3.91, p=0.056, ES=0.10] with cortical thickness reducing with increase in age. There was no significant region X diagnosis interaction [F(1,34)=0.83, p=0.37, ES=0.024]. Independent t-tests of regional measures adjusted for age and global thickness revealed significant reduction in thickness at right circular superior sulcus [t(1,36)=2.35, p=0.02] and right circular anterior sulcus [t(1,36)=3.19, p=0.003]. The results are tabulated in table 2.

Contribution of phase resetting to evoked signal

In controls, T-phase significantly predicted T-mean [F(1,18)=7.136, p=0.016, R^2=0.284]. In schizophrenia, T-phase did not predict the T-mean [F(1,16)=1.079, p=0.314, R2=0.06] and T-mean was significantly reduced when compared to controls [F(1,36)=9.707, p=0.004] (figure 2). The difference in the beta coefficients between patients (ß=0.033, SEM=0.032) and controls (ß=0.088, SEM =0.033) was not statistically significant (p=0.24). The correlation between the phase locking and mean evoked activity in the two groups is plotted as figure 3.

Phase resetting and SN thickness in schizophrenia

Theta phase emerged as a robust predictor of SN thickness in schizophrenia [F(1,14)=17.17, p=0.001, ES=0.55]. Global cortical thickness, as expected, also

Table 1. Summary of the demographic data for patients and controls.

Parameter	*Patients (n=18) Mean (SD)*	*Controls (n=20) Mean (SD)*	*Independent samples t test*
Age	22.77 (4.88)	24 (5.00)	t=–0.76, p=0.45
Parental socio-economic status (NS-SEC)	2.55 (1.54)	1.95 (1.31)	t=1.31, p=0.20
Quick Test score	89.16	102.8	t=–2.91, p=0.006
Handedness index	10.89 (2.11)	11.60 (0.68)	t=–1.37, p=0.19
SSPI total	12.22	NA	
SSPI reality distortion	2.22	NA	
SSPI psychomotor poverty	2.66	NA	
SSPI disorganisation	0.61	NA	

NS-SEC: National statistics-socio economic status, SSPI: Signs and symptoms in psychotic illness scale, NA: Not available

Table 2. Salience Network thickness (in millimetres) adjusted for age and global mean thickness.

	Left hemisphere			*Right hemisphere*		
	Controls	*Patients*		*Controls*	*Patients*	
	adjusted mean (SE)	*adjusted mean (SE)*		*adjusted mean (SE)*	*adjusted mean (SE)*	
Brain region			*Effect size*			*Effect size*
Anterior cingulate cortex	2.41 (0.05)	2.43 (0.05)	–0.09	2.73 (0.04)	2.65 (0.04)	0.49
Short insular gyrus (anterior)	3.82 (0.05)	3.78 (0.05)	0.22	3.85 (0.05)	3.73 (0.06)	0.48
Circular sulcus anterior	2.85 (0.05)	2.86 (0.05)	–0.05	3.15 (0.06)	2.84 (0.06)	**1.14****
Circular sulcus superior	2.53 (0.04)	2.47 (0.04)	0.35	2.56 (0.03)	2.44 (0.03)	**0.85***

Positive values of effect sizes indicate a reduction in insular thickness in schizophrenia compared to controls. **p<0.001, *p<0.01. SE: Standard error

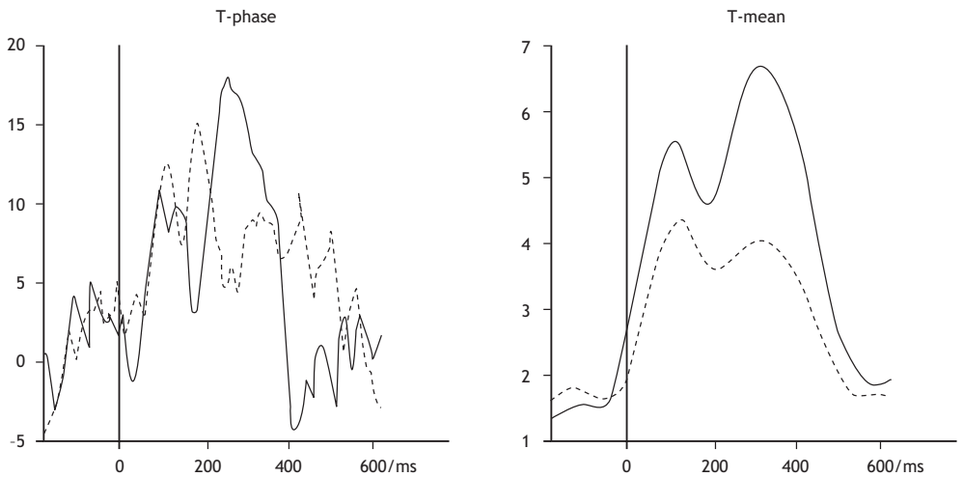

Figure 2. T-Phase and T-Mean in patients with schizophrenia and controls. Grand-average of T-mean and T-phase in the control (solid line) and patient (dashed line) group. The vertical line denotes target stimulus onset.

emerged as a significant predictor of SN thickness [F(1,14)=25.16, p<0.001, ES=0.64]. Age was not a significant covariate [F(1,14)=1.61, p=0.23, ES=0.10] in this model.

Significant effect was noted for regions X T-Phase interaction [F(1,14)=8.77, p=0.01, ES=0.39]. Further analysis of the parcellations on either hemisphere after controlling for mean whole brain thickness revealed that largest association of diminished thickness and phase resetting was noted in the left short insular gyrus (r=0.765 p<0.001) followed by the right superior circular sulcus (r=0.603 p=0.01) and the left

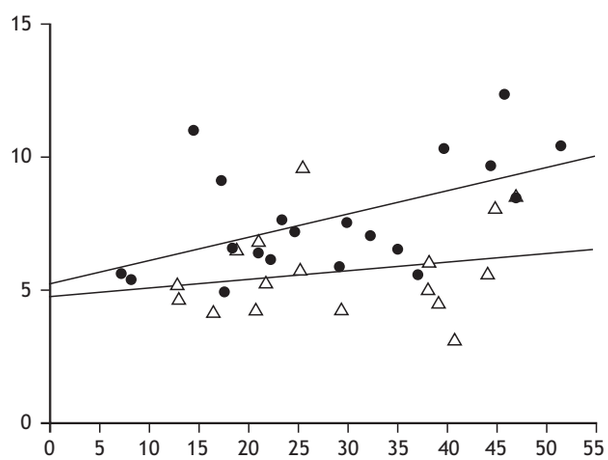

Figure 3. Relationship between Phase Reset and Evoked Activity. Scatter plot of the correlation between theta band T-phase (x-axis) and T-mean (y-axis) in the patient (triangles) and control (dots) group. (Time window: 0 to 600 ms).

superior circular sulcus (r=0.486 p<0.05). A trend towards significant correlation was seen in the right short insular gyrus (r=0.448 p=0.07). Neither left nor right anterior cingulate showed significant correlation in the post-hoc tests (left anterior cingulate r=0.11 p=0.67, right anterior cingulate r=0.002 p=0.99). Effect sizes (Pearson's correlation coefficients) from the post-hoc analysis are shown in figure 4.

In healthy controls, theta phase was not a significant predictor of the SN thickness [F(1,16)=0.525, p=0.48, ES=0.03].

Discussion

Using MRI morphometric analysis of cortical thickness, we have firstly shown that there is a significant loss of thickness of regions that constitute the Salience Network in patients with schizophrenia. Using EEG recording of auditory oddball target detection task we have also shown that while in healthy controls, the expected relationship between phase resetting and evoked electrical activity is observed, in schizophrenia the theta phase resetting is a weak predictor of the activity evoked by attending to a target stimulus, though the difference between the groups did not reach statistical significance. Finally, bringing together the EEG oscillatory analysis and the MRI structural analysis, we have shown that in patients with schizophrenia the grey matter reduction in the Salience Network is associated with the inefficient phase resetting of theta oscillations.

Salience network in schizophrenia

We have identified a significant reduction in the grey matter thickness of regions constituting the Salience Network in patients as predicted. This reduction is more pronounced for the insular regions on the right hemisphere. Our finding is broadly consistent with the meta-analyses of VBM studies showing that the most prominent grey matter deficits in schizophrenia are in bilateral insula and ACC.[1,2] Studies using manual tracing or parcellation tech-

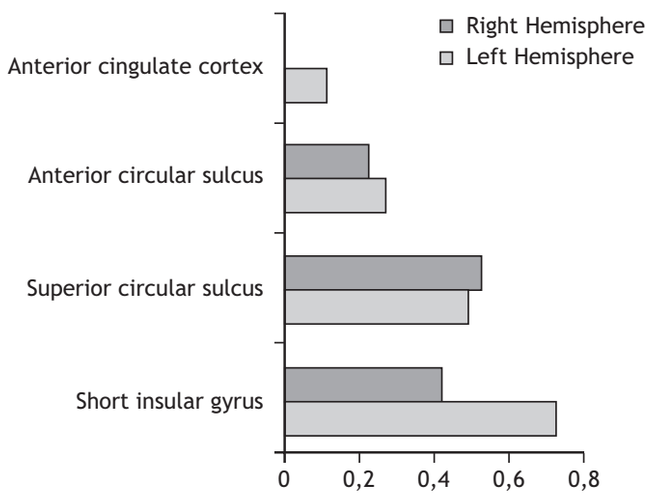

Figure 4. SN Thickness and Phase Reset. Pearson's correlation coefficients between regional thickness measures across the four parcellations of the Salience Network adjusted for global thickness and the frontal theta phase resetting measure (T-phase) in patients with schizophrenia. Statistically significant associations were present for right and left superior circular sulcus and left short insular gyrus. A trend towards positive correlation was seen in right short insular gyrus.

niques have generally concurred with the finding of grey matter reduction in the insula despite some inconsistencies (see Palaniyappan and Liddle[3] for a review).

Despite numerous investigations establishing the importance of ICNs in healthy individuals, only few have explored them in schizophrenia.[40] Accumulating evidence indicates that patients with schizophrenia and their relatives exhibit difficulties in deactivating the default network during working memory tasks, resulting in tonic hyperactivation of the default network.[41] Indirect evidence for involvement of various regions that constitute the salience network during attentional tasks in schizophrenia comes from oddball experiments in fMRI[13] and EEG.[42] More recently, using Independent Component Analysis of fMRI during somatosensory stimulation, White et al[43] have demonstrated a significant loss of the SN activation and associated DMN deactivation during perceptual processing in patients with schizophrenia.

Phase resetting

Our data shows that in healthy controls, theta phase resetting strongly predicts evoked activity. Phase resetting is a promising neurophysiological candidate for effective transmission of information regarding salience of environmental stimuli.[44] A significant portion of variability in signal detection is ascribed to the oscillatory phase preceding a stimulus.[23] Phase resetting has been shown to be a mechanism of optimising the processing of incoming information.[45] In addition, Lakatos et al using intracortical field potential recording in macaques have recently shown a direct effect of phase resetting in supramodal attentional control.[24] Resetting ongoing oscillatory phase to an "ideal phase" upon presentation of salient environmental stimuli may prepare various cortical regions to be in an optimum receptive state for cognitive processing. Phase resetting will tend to establish a consistent relationship between the phase of ongoing oscillations and the additive neural activity elicited by the stimulus. Depending on whether this relationship is one of mutual reinforcement or antagonism, the net amount of neural activity in a particular brain region might be either increased or decreased. Hence, while some regions are "deactivated", some others may be "activated". Thus phase resetting may act as a high-level cognitive control mechanism reinforcing synchronous activity in brain regions required for processing the stimulus while deactivating (or switching off) cortical nodes that might interfere with the processing of current stimulus. It is worth noting that a reduction in phase resetting of low frequency oscillations has previously been reported in patients with schizophrenia.[25,28] Given the role of phase resetting in attentional control, these abnormalities are likely to be associated with the cognitive deficits noted in schizophrenia.

Insula and salience detection

We have shown that theta phase resetting is proportionate to the thickness of Salience Network in schizophrenia. This relationship is more pronounced with insular cortex than to anterior cingulate cortex. The role of insula in salience detection and switching access between brain networks has recently been reviewed by Menon and Uddin.[46] To facilitate the description of the function of the salience network, we have introduced the concept of proximal salience.[3] External or internal (bodily) events attain proximal salience when they generate a momentary state of neural activity within the salience network that results in updating of expectations and, in some cases, initiation or modification of action. To our knowledge, the physiological mechanism behind the switching ascribed to insula is hitherto unexplored. Our data shows that inefficient phase resetting of frontal theta oscillatory activity is related to abnormalities in insular thickness. This suggests that insula could act as a phase regulator that enables switching between the relevant networks via direct modulation of theta oscillations. Shulman et al[47] showed that insula, along with other regions in the SN, is highly likely to be the control region that modulates attentional shift to unexpected stimuli.

We have previously shown that the structure of the SN is related to the symptom burden in schizophrenia.[48,49] Given that salience dysregulation is a key feature of reality distortion seen in schizophrenia, our current findings reinforce our previous proposition that insula pays a central role in generation of psychotic symptoms.[3] Further, the absence of a significant relationship between theta phase and SN

thickness in healthy controls suggests that the relationship observed in patients is due to pathological variation in the grey matter of the SN.

Limitations

Our study sample is comprised entirely of males. Gender differences in brain structure have been shown though the effect of such differences on information processing deficits seen in schizophrenia remains unclear. All of our patients were medicated with antipsychotics at the time of participation. The effect of antipsychotic on brain structure is debatable. The most robust finding is increased basal ganglia volume, while there is conflicting evidence regarding other brain regions.[50] The relationship between antipsychotics and the brain oscillatory activity is currently unclear, though evidence from meta-analysis of P300 studies suggests that the antipsychotic does not account for reduced evoked activity.[51] A decrease in evoked low frequency oscillations has been noted in both medicated patients with schizophrenia and unmedicated siblings of the patients.[52,53] This suggests that medications cannot fully explain theta oscillatory abnormalities noted in schizophrenia. While our study focused upon the Salience Network, we cannot exclude the possibility that abnormalities in other brain regions also contribute to impaired phase resetting.

Conclusion

Although several studies have investigated separately the deficits in insular grey matter, oscillatory activity, and attentional salience in schizophrenia, this is the first study bringing together these findings. Present results show that abnormalities of theta phase resetting and hence oscillatory synchrony in schizophrenia could be mediated by the insula, which forms the core of the intrinsic salience network.

Πάχος φλοιού και επαναρύθμιση της φάσης ταλάντωσης: Προτεινόμενος μηχανισμός δυσλειτουργίας του διακριτικού δικτύου στη σχιζοφρένεια

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Η σχιζοφρένεια χαρακτηρίζεται τόσο από ηλεκτροφυσιολογικές ανωμαλίες όσο και από σταθερές αλλαγές στη δομή της φαιάς ουσίας του φλοιού. Εντούτοις, η σχέση μεταξύ των δύο αυτών παρατηρήσεων είναι σε μεγάλο βαθμό άγνωστη. Οι δομικές μεταβολές που αναφέρονται στη σχιζοφρένεια περιλαμβάνουν μείωση του όγκου της φαιάς ουσίας, του πάχους και της επιφάνειας του φλοιού σε διάφορες περιοχές, πιο συχνά δε στη νησίδα και τον φλοιό του πρόσθιου προσαγωγίου. Αυτές οι δύο περιοχές αποτελούν ένα εγγενές κύκλωμα του εγκεφάλου που είναι γνωστό ως «Διακριτικό Δίκτυο» (Salience Network) το οποίο παίζει βασικό ρόλο στην επεξεργασία ερεθισμάτων. Η επεξεργασία ερεθισμάτων προκαλεί δραστηριότητα στο ηλεκτροεγκεφαλογράφημα (EEG). Η επαναφορά της φάσης των συνεχιζόμενων ταλαντώσεων συμβάλλει σε αυτήν την πρόκληση δραστηριότητας. Οι νευρωνικές ταλαντώσεις παίζουν καίριο ρόλο στην εγκεφαλική επιστράτευση κατά τη διάρκεια νοητικών δοκιμασιών, και αλλαγές στη φάση της ταλάντωσης μπορούν να τροποποιήσουν την ευερεθιστότη-

τα του φλοιού και τη μετάβαση μεταξύ διαφόρων νοητικών καταστάσεων. Σε επίπεδο δικτύου, αυτή η μετάβαση ή αλλαγή θεωρείται ότι πραγματοποιείται από το Διακριτικό Δίκτυο. Στην παρούσα μελέτη, διερευνήθηκε η σχέση μεταξύ του πάχους του φλοιού του Διακριτικού Δικτύου (μέτρηση με μαγνητική τομογραφία) και του βαθμού της επαναρύθμισης της φάσης που παρατηρήθηκε κατά τη διάρκεια μιας «δοκιμασίας παραδοξότητας» (oddball task-μετράται με ΗΕΓ) σε 18 ασθενείς με σχιζοφρένεια υπό θεραπεία και σε σταθερή κλινική φάση, και 20 υγιείς μάρτυρες αντίστοιχης ηλικίας και φύλου. Καταγράψαμε μια μέτρηση της μερικής επαναρύθμισης της φάσης μετά από ερέθισμα, και μια δεύτερη μέτρηση που εκπροσωπεί τη μέση προκλητή δραστηριότητα, χρησιμοποιώντας τις μεθόδους που έχουν προτείνει οι Martinez-Montes. Χρησιμοποιώντας την ανάλυση των μαγνητικών τομογραφιών, πρώτα δείξαμε ότι υπάρχει σημαντική μείωση στο πάχος του φλοιού σε περιοχές που απαρτίζουν το Διακριτικό Δίκτυο στη σχιζοφρένεια. Η ανάλυση των ηλεκτροεγκεφαλογραφημάτων απεκάλυψε ότι στους υγιείς μάρτυρες, ενώ παρατηρείται η αναμενόμενη σχέση μεταξύ της επαναρύθμισης της φάσης και της προκλητής ηλεκτρικής δραστηριότητας, αντιθέτως στους ασθενείς με σχιζοφρένεια η επαναφορά της φάσης θα είναι ασθενής προγνωστικός δείκτης της δραστηριότητας που προκαλείται από την προσοχή σε ένα ερέθισμα-στόχο, αν και η διαφορά μεταξύ των ομάδων δεν είχε στατιστική σημαντικότητα στο παρόν δείγμα. Επιπροσθέτως, στους ασθενείς με σχιζοφρένεια το μειωμένο πάχος του Διακριτικού Δικτύου συσχετίζεται με την αναποτελεσματική επαναφορά της φάσης των ταλαντώσεων θ. Τα ευρήματά μας υποδηλώνουν ότι η μείωση της φαιάς ουσίας που παρατηρείται στο Διακριτικό Δίκτυο σε ασθενείς με σχιζοφρένεια έχει σημαντικές λειτουργικές συνέπειες. Ειδικότερα, το δομικό ελάττωμα στη νησίδα που παρατηρείται στη σχιζοφρένεια είναι πιθανόν να συνδέεται με λιγότερο αποδοτική επιστράτευση των κυκλωμάτων του εγκεφάλου για την επεξεργασία πληροφοριών. Αυτό συνεπάγεται έναν πιθανό μηχανισμό με τον οποίο διαταραχές στο εγγενές Διακριτικό Δίκτυο μπορούν να οδηγήσουν σε μια γενική διαταραχή στη διακριτική λειτουργία στη σχιζοφρένεια.

Λέξεις ευρετηρίου: Διακριτικό δίκτυο, επαναφορά φάσης, ταλαντώσεις, νησίδα, προσαγώγιο.

References

1. Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL et al. Meta-Analysis of Gray Matter Anomalies in Schizophrenia: Application of Anatomic Likelihood Estimation and Network Analysis. *Biologic Psychiatry* 2008 64:774–781
2. Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *Am J Psychiatry* 2008, 165:1015–1023
3. Palaniyappan L, Liddle PF. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. *J Psychiatry Neurosci* 2012, 37:17–27
4. Borgwardt S, McGuire P, Fusar-Poli P. Gray matters! - Mapping the transition to psychosis. *Schizophr Res* 2011, 133:63–67
5. Fusar-Poli P, Radua J, McGuire P, Stefan B. *Neuroanatomical Maps of Psychosis Onset: Voxel-wise Meta-Analysis of Antipsychotic-Naive VBM Studies*. Schizophrenia Bulletin (Internet). 2011 Nov 10 (cited 2011 Nov 24); Available from: http://schizophreniabulletin.oxfordjournals.org/content/early/2011/11/09/schbul.sbr134.abstract
6. Smieskova R, Fusar-Poli P, Aston J, Simon A, Bendfeldt K, Lenz C et al. Insular Volume Abnormalities Associated with Different Transition Probabilities to Psychosis. *Psychologic Med* 2011, First View:1–13
7. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H et al. Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *J Neurosci* 2007 27:2349–2356
8. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proceed Nat Acad Sci USA* 2001, 98:676–682
9. Gusnard DA, Raichle ME. Searching for a baseline: Functional imaging and the resting human brain. *Nat Rev Neurosci* 2001, 2:685–694
10. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceed Nat Acad Sci USA* 2003, 100:253–258
11. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceed Nat Acad Sci USA* 2008, 105:12569–12574
12. Laurens KR, Kiehl KA, Ngan ETC, Liddle PF. Attention orienting dysfunction during salient novel stimulus processing in schizophrenia. *Schizophrenia Research* 2005, 75:159–171
13. Liddle PF, Laurens KR, Kiehl KA, Ngan ETC. Abnormal function of the brain system supporting motivated attention in medicated patients with schizophrenia: an fMRI study. *Psychol Med* 2006 36:1097–1108

14. Cortipas M, Corral M-J, Garrido G, Garolera M, Pajares M, Escera C. Reduced novelty-P3 associated with increased behavioral distractibility in schizophrenia. *Biologic Psychol* 2008, 78:253–260
15. Gouzoulis-Mayfrank E, Balke M, Hajsamou S, Ruhrmann S, Schultze-Lutter F, Daumann J et al. Orienting of attention in unmedicated patients with schizophrenia, prodromal subjects and healthy relatives. *Schizophr Res* 2007, 97:35–42
16. Gooding DC, Braun JG, Studer JA. Attentional network task performance in patients with schizophrenia-spectrum disorders: Evidence of a specific deficit. *Schizophr Res* 2006 88: 169–178
17. Wang K, Fan J, Dong Y, Wang C-qing, Lee TMC, Posner MI. Selective impairment of attentional networks of orienting and executive control in schizophrenia. *Schizophr Res* 2005, 78: 235–241
18. Sauseng P, Klimesch W, Gruber WR, Hanslmayr S, Freunberger R, Doppelmayr M. Are event-related potential components generated by phase resetting of brain oscillations? A critical discussion. *Neuroscience* 2007, 146:1435–1444
19. Klimesch W, Sauseng P, Hanslmayr S, Gruber W, Freunberger R. Event-related phase reorganization may explain evoked neural dynamics. *Neurosci Biobehav Rev* 2007, 31:1003–1016
20. Sauseng P, Klimesch W. What does phase information of oscillatory brain activity tell us about cognitive processes? *Neurosci Biobehav Rev* 2008, 32:1001–1013
21. Melloni L, Molina C, Pena M, Torres D, Singer W, Rodriguez E. Synchronization of Neural Activity across Cortical Areas Correlates with Conscious Perception. *J Neurosci* 2007 27: 2858–2865
22. Palva S, Linkenkaer-Hansen K, Naatanen R, Palva JM. Early Neural Correlates of Conscious Somatosensory Perception. *J Neurosci* 2005, 25:5248–5258
23. Busch NA, Dubois J, VanRullen R. The Phase of Ongoing EEG Oscillations Predicts Visual Perception. *J Neurosci* 2009 29:7869–7876
24. Lakatos P, O'Connell MN, Barczak A, Mills A, Javitt DC, Schroeder CE. The Leading Sense: Supramodal Control of Neurophysiological Context by Attention. *Neuron* 2009, 64:419–430
25. Brockhaus-Dumke A, Mueller R, Faigle U, Klosterkoetter J. Sensory gating revisited: Relation between brain oscillations and auditory evoked potentials in schizophrenia. *Schizophrenia Research* 2008, 99:238–249
26. Doege K, Bates AT, White TP, Das D, Boks MP, Liddle PF. Reduced event-related low frequency EEG activity in schizophrenia during an auditory oddball task. *Psychophysiology* 2009, 46:566–577
27. Schmiedt C, Brand A, Hildebrandt H, Basar-Eroglu C. Event-related theta oscillations during working memory tasks in patients with schizophrenia and healthy controls. *Cognitive Brain Research* 2005, 25:936–947
28. Doege K, Jansen M, Mallikarjun P, Liddle EB, Liddle PF. How much does phase resetting contribute to event-related EEG abnormalities in schizophrenia? Neuroscience Letters [Internet]. 2010 Jun (cited 2010 Jun 28) Available from: http://sciencedirect.linkpc.net/science
29. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC, 1994
30. Ammons RB, Ammons CH. *Quick Test,* 1962
31. Liddle PF, Ngan ETC, Duffield G, Kho K, Warren AJ. Signs and Symptoms of Psychotic Illness (SSPI): a rating scale. *Br J Psychiatry* 2002, 180:45–50
32. Rose D, Pevalin DJ. *A Researcher's Guide to the National Statistics Socio-economic Classification*. London, Sage Publications, 2003
33. Annett M. A classification of hand preference by association analysis. *Br J Psychol* 1970, 61:303–321
34. Oostenveld R, Praamstra P. The five percent electrode system for high-resolution EEG and ERP measurements. *Clin Neurophysiol* 2001, 112:713–719
35. Gratton G, Coles MGH, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 1983, 55:468–484
36. Martvnez-Montes E, Cuspineda-Bravo ER, El-Deredy W, Sanchez-Bornot JM, Lage-Castellanos A, Valdıs-Sosa PA. Exploring event-related brain dynamics with tests on complex valued time-frequency representations. *Stat Med* 2008, 27:2922–2947
37. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceed Nat Acad Sci USA* 2000, 97:11050–11055
38. Destrieux C, Fischl B, Dale A, Halgren E. A sulcal depth-based anatomical parcellation of the cerebral cortex. *NeuroImage* 2009, 47(Suppl 1):S151
39. Vogt BA, Berger GR, Derbyshire SWG. Structural and functional dichotomy of human midcingulate cortex. *Eur J Neurosci* 2003, 18:3134–3144
40. Williamson P. Are Anticorrelated Networks in the Brain Relevant to Schizophrenia? *Schizophr Bull* 2007, 33:994–1003
41. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proceed Nat Acad Sci USA* 2009, 106:1279–1284
42. Kiehl KA, Liddle PF. An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia. *Schizophr Res* 2001, 48:159–171
43. White TP, Joseph V, Francis ST, Liddle PF. Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. *Schizophr. Res* 2010, 123:105–115
44. Kayser C. Phase Resetting as a Mechanism for Supramodal Attentional. *Control Neuron* 2009, 64:300–302
45. Rutishauser U, Ross IB, Mamelak AN, Schuman EM. Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature* 2010, 7290:903–907
46. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct (Internet). 2010 May 29 (cited 2010 Jun 10); Available from: http://www.ncbi.nlm.nih.gov/pubmed/20512370
47. Shulman GL, Astafiev SV, Franke D, Pope DLW, Snyder AZ, McAvoy MP et al. Interaction of Stimulus-Driven Reorienting and Expectation in Ventral and Dorsal Frontoparietal and Basal Ganglia-Cortical Networks. *J Neurosci* 2009, 29:4392–4407
48. Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF. Reality distortion is related to the structure of the salience network in schizophrenia. *Psychol Med* 2011, 41:1701–178

49. Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF. Regional contraction of brain surface area involves three large-scale networks in schizophrenia. *Schizophr Res* 2011, 129: 163–168

50. Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J et al. The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia? A systematic review. *Curr Pharm Des* 2009, 15:2535–2549

51. Jeon YW, Polich J. Meta-analysis of P300 and schizophrenia: Patients, paradigms, and practical implications. *Psychophysiology* 2003, 40:684–701

52. Liddle PF, Bates AT, Plodowski AM, Groom MJ, Jackson GM, Hollis CP. Aberrant low frequency oscillatory activity in adolescent onset schizophrenia and siblings on an error monitoring task. *Schizophr Res* 2006, 81:13

53. Hong LE, Summerfelt A, Mitchell BD, McMahon RP, Wonodi I, Buchanan RW et al. Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate. *Arch Gen Psychiatry* 2008, 65:1008–1016

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Research article
Ερευνητική εργασία

Psychometric properties of WHOQOL-BREF in clinical and healthy Greek populations: Incorporating new culture-relevant items

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The present study examines main psychometric properties of the World Health Organisation (WHO) quality of life (QoL) instrument, the WHOQOL-BREF with the inclusion of four national items. Participants were 425 adult native Greek speaking, grouped into patients with physical disorders, psychiatric disorders and healthy individuals. Participants were administered WHOQOL-BREF and 23 national items, the General Health Questionnaire (GHQ-28) and the Life Satisfaction Index (LSI). Confirmatory factor analysis produced acceptable fit values for the original model of 26 items within the four WHOQOL domains: physical health, psychological health, social relationships and environment. Testing for the fit of national items within this model, the results indicated four new items with the most satisfactory fit indices and were thus included forming a 30-items version. The national items refer to: (a) nutrition, (b) satisfaction with work (both loaded in the physical health domain), (c) home life and (d) social life (both loaded in the social relationships domain). Statistical tests were applied to the 26- and 30-items versions producing satisfactory results, with the 30-items version showing slightly better values. Furthermore, results on the 30-items version included: (a) internal consistency, which was found satisfactory, with alpha values ranging from α=0.67–0.81, while the inclusion of new items produced higher alpha values in physical health and social relationships domains, (b) construct validity with good item–domain correlations, as well as strong correlations between domain scores, (c) convergent validity, which was very satisfactory, showing good correlations with GHQ-28 and LSI, (d) discriminant validity, showing instrument's ability to detect QoL differences between healthy and unhealthy participants, and between physically

ill and psychiatric patients, and (e) test-retest reliability, with ICC scores in excess of 0.80 obtaining for all domains. The WHOQOL-BREF Greek version was found to perform well with sick and healthy participants, demonstrating satisfactory psychometric properties. Use of the instrument may be recommended for clinical and general populations, for service or intervention evaluation, as well as for cross-cultural clinical trials.

Key words: WHOQOL-BREF, validity, reliability, quality of life, physical illness, mental disorders.

Introduction

Measurements of quality of life (QoL) are increasingly used today as part of routine clinical care and reappraisal, across different groups of patients with physical or mental disorders and across different countries.[1–6] QoL measurement can provide health carers with valuable information regarding the needs of patients and the effects of interventions.

Besides patient-centred use, QoL measurements are systematically applied to monitor outcomes from clinical trials in multinational studies. So, QoL instruments are used for various aims and in different countries, but they need to be suitable, as they can be culture-specific or disease-specific restricting validity of cross-cultural comparisons across large patient groups.[7] Language and culturally validated measurements are thus needed to assess the impact of disorders and treatments across different settings and patient groups. Addressing these issues, the World Health Organisation (WHO) produced a generic QoL instrument, which can be tested in different languages and clinical or social settings, as to become suitable for systematic cross-cultural health-related Qol measurement.[8–9]

WHOQOL-BREF: A brief historical account

Introduced as an easily administered instrument for measuring therapeutic outcomes, the WHOQOL-BREF is an abbreviated 26-items version of WHOQOL-100, developed by the World Health Organization.[9–10] Items have been selected from 100-items form of WHOQOL on the basis of statistical criteria.[11–12]

WHOQOL-BREF consists of 24 items corresponding to 24 QoL (thematic) facets, and two items comprising an overall quality of life/general health facet. Items are organized into 4 domains: (1) physical health, (2) psychological health, (3) social relationships and (4) environment. The 4-domain model was produced after merging two of the original six WHOQOL-100 domains, i.e. Level of Independence and Spirituality domains and has been tested and found consistent with empirical results of WHOQOL-100 field studies.[10–11] More recently, an international field trial of the WHOQOL-Group in 23 countries indicated that WHOQOL-BREF has good to excellent psychometric properties and is identified as a cross-culturally valid instrument for assessing QoL.[12] WHOQOL is based on cross-cultural methodology supporting the inclusion of extra national items that can be generated by focus groups in each country or language, and can be added to the core items in order to acquire conceptual equivalence and accommodate the rich, semantic and cultural variations of QoL across different language versions.[13–14] WHOQOL-BREF has been tested as a health-related QoL measurement system, showing suitability in cross-linguistic and cross-cultural studies involving different patient groups.

Since its development, WHOQOL-BREF has been translated and validated into several languages, among which are: Argentina,[15] India,[16] Thailand,[17] Australia,[18] Turkey,[19] Denmark,[20] Korea,[21] Malaysia,[22] Poland,[23] Israel,[24] Taiwan,[25] China,[26] India,[27] Ireland,[28] Norway.[29]

The purpose of the current study was to examine psychometric properties of WHOQOL-BREF and determine the suitability of national items within the original model. For this purpose, following the guidelines of WHO, several focus groups were conducted with patients and health carers resulting in 23 new national items.[30–31]

Material and method

Patient respondents were recruited from primary care, rehabilitation and hospital settings. Healthy respondents came from administrative personnel in the public sector.

Following the WHO protocol for the development of WHOQOL instruments in new centers,[32] a sample of 425 individuals participated in the study, consisting of patients with physical illness (n=234), patients with mental disorders (n=124), and healthy individuals (n=67).

Physically ill individuals were under treatment for the last 5 years diagnosed with chronic, moderate or severe hypertension (n=139), or with different forms of cancer (n=95), (no cases in palliative care or undergoing chemotherapy within the last year). Patients were consecutive visits at relevant outpatient units in two public General Hospitals.

Psychiatric patients consisted of chronic schizophrenic outpatients (n=87), attending community mental health services, or were in-patients with alcohol abuse/dependence (n=37), consecutively admitted for a 5-week detoxification therapy.[33] All psychiatric participants were recruited from the University of Athens Department of Psychiatry, and were diagnosed according to DSM-IV criteria.[34]

Healthy participants were randomly selected from administrative employees of public services, reporting being free from disease at the time of the study.

All subjects participated on a voluntary basis and were provided with informed consent forms, being free to withdraw at any time and for any reason.

Instruments

In addition to administering WHOQOL-BREF and national items, participants completed the General Health Questionnaire (GHQ-28) and Life Satisfaction Index (LSI):

a. WHOQOL-BREF pilot version

The 26-items version is rated on a 5-point Likert scale, with higher scores indicating positive item assessment. All scores were transformed to a 0–100 scale, in accordance with the WHO guidelines.[35] The WHOQOL-100 items form including WHOQOL-BREF items underwent a rigorous translation, back translation and cross-examination by bilingual subjects.[30–31] Furthermore, investigation was performed on cultural and linguistic equivalence of WHOQOL measurement using focus groups methodology.[30–31] As a result, 23 national items were produced which were formulated to fit the WHOQOL-BREF questioning format and were administered in a separate section. Testing initially the WHOQOL-100, satisfactory psychometric properties were found in healthy and patient groups within the specific cultural context.[33,36]

b. Life Satisfaction Index (LSI)

LSI is a 13-items questionnaire, validated with greek samples.[37] It is a generic, self-report measure of satisfaction with various aspects of life: physical state, mental state, psychological health, occupation, financial status, relationships with the partner, sexual life, family life, role in the family, friends and acquaintances, hobbies, physical appearance, and general QoL.[38] A higher total score is indicative of greater life satisfaction.

c. General Health Questionnaire (GHQ-28)

It is a well known self-report measure of common psychiatric symptoms widely used to identify short term changes in mental health and is often used as a screening instrument for detecting mental disorders in clinical and non-clinical populations.[39] Psychometric properties of the 28-item Greek version are reported as satisfactory.[40] It consists of four sub-scales measuring: (a) somatic symptoms, (b) anxiety/insomnia, (c) social dysfunction, and (d) severe depression. The GHQ-28 employs a response scale ranging from 0 to 3, with higher values indicating the worst health status. Scores were reversed for consistency of reference with other measures of the present study, so higher scores indicate a more positive self-assessment of health.

Procedure

The above instruments were administered once. In addition, healthy participants were invited to complete the questionnaire within 3–4 weeks in order to perform test/re-test analysis.[32]

Statistical analysis

Data were analysed using SPSS for Windows, Version 13.0 (SPSS, Chicago, IL, USA). Analysis included: confirmatory factor analysis and testing for inter-

nal consistency, construct validity, convergent validity, discriminant validity and test-retest reliability.[41]

Results

Demographic characteristics

Sociodemographic characteristics of patient and healthy participants are displayed in table 1.

Structure of the instrument

Confirmatory factor analysis (CFA) at item level was performed using the 26 items values corresponding to 24 facets and 2 items referring to the global facet of QoL/health. The results strongly supported the structure of WHOQOL-BREF with all items loading onto four domains originally assigned to. Furthermore, 23 national items were introduced into the model and testing highlighted 4 items with the best fit in the model. These items refer to new thematic facets: (1) nutrition; (2) work satisfaction; (3) home-life; and (4) social life. The thematic content of these facets is described in the respective publication including the translation of the original domains and facets of the WHOQOL instrument.[42] The 4 new items loaded on two of the existing domains supporting the 4-domain structure table 2). Specifically, the two items referring to nutrition and work satisfaction loaded onto the WHOQOL-BREF physical health domain, whilst the other two items referring to home-life and social life loaded onto the WHOQOL-BREF social relationships domain. Additionally, the comparative fit index (CFI) on the four domain model was well above 0.9 (CFI=0,981). Based on these results, a 30-items version including 4 national items was produced (Appendix I). Next, the 30-items and the original 26-items versions underwent statistical analysis for internal consistency.

Internal consistency

Calculation of Cronbach's alpha coefficient per domain was performed, which resulted in satisfactory alpha values ranging from 0.67–0.81 for the 30-items version (table 3). Slightly less satisfactory results were produced for the 26-items version, particularly in relation to social relationships domain (table 4).

Construct validity

Pearson coefficient (r) was performed between item-domain scores in the total sample of participants (N=425). Results demonstrated good item-domain correlations and strong correlations between all total domains scores, particularly between physical health, psychological health and social relationships. Moderate correlations were identified between environment domain score and all other domains. In overall, the values confirm the construct validity of the instrument (table 5). (Low correlations range from 0.1–0.3; moderate from 0.3–0.5 and high >0.5).

Convergent validity

It was hypothesized that WHOQOL-BREF domain scores would be closely related to scores obtained from the sub-scales of the GHQ-28 and the total score of the LSI instrument. In particular, the WHOQOL-BREF physical and psychological health

Table 1. Demographic characteristics of the physically ill, the psychiatrically ill and the healthy participants (N=425).

	Physically ill N=234		*Psychiatrically ill N=124*		*Healthy N=67*	
	N (%)	*Mean (SD)*	*N (%)*	*Mean (SD)*	*N (%)*	*Mean (SD)*
Mean age (years)		60.71 (11.11)		40.79 (11.88)		32.75 (8.12)
Gender: Male	75 (32.1%)		83 (66.9%)		20 (29.9%)	
Female	159 (67.9%)		41 (33.1%)		47 (70,1%)	
Education (years)		9.15 (3.83)		11.25 (3.55)		14.97 (2.65)
Marital status:						
Single	17 (7,3%)		72 (58.1%)		30 (44.8%)	
Married/Cohabitating	168 (71,8%)		35 (28,2%)		34 (50.7%)	
Separated/Divorced/Widowed	49 (20,9%)		17 (13,7%)		3 (4.5%)	

Table 2. Confirmatory factor analysis (CFA) on WHOQOL-BREF 30-items version.

WHQOL-BREF Domains	*Number-Item**	*Factor loadings*
Overall QoL/general health	1	0.73
	2	0.53
Physical health (including the domain "level of independence")	3	0.36
	10	–0.73
	16	–0.48
	15	–0.69
	17	–0.83
	4	0.42
	18	–0.83
	N1**	–0.48
	N4**	–0.49
Mental health (including the domain "spirituality/religion/personal beliefs")	5	0.60
	7	0.58
	19	0.80
	11	0.45
	26	–0.61
	6	0.69
Social relationships	20	0.74
	22	0.60
	21	0.52
	*N2***	0.72
	*N3***	0.60
Environment	8	0.18
	23	0.63
	12	0.48
	24	0.51
	13	0.40
	14	0.33
	9	0.50
	25	0.60

*Item number as presented in the administration form, ***N*=National items (Appendix I)

Table 3. Internal consistency (Cronbach's alpha) of the 30-items version.

WHOQOL-BREF Domains	*alpha (α)*
Physical health	0.81
Mental health	0.79
Social relationships	0.76
Environment	0.67
Overall QoL/general health	0.89

Table 4. Internal Consistency (Cronbach's alpha) of the 26-items version.

WHOQOL-BREF Domains	*alpha (α)*
Physical health	0.80
Mental health	0.79
Social relationships	0.65
Environment	0.66
Overall QoL/general health	0.87

domains would correlate with all four GHQ-28 sub-scales, while social relationships domain would demonstrate strong correlation with the total LSI score due to similarity in their content. In accordance with our expectations, a considerable number of correlations in the total sample of 425 participants were found to be moderate to strong. In addition, strong correlations between the WHOQOL-BREF overall QoL/general health facet and the GHQ-28 sub-scales were identified (table 6).

Table 5. Correlations between WHOQOL-BREF domain scores (Pearson's r) in the total sample.

	Physical health	*Psychological health*	*Social relationships*	*Environment*	*Overall QoL/general health*
Physical health	1.00	0.73*	0.55*	0.36*	0.67**
Mental health	0.73*	1.00	0.65*	0.34	0.63**
Social relationships	0.55*	0.65*	1.00	0.37	0.60**
Environment	0.36*	0.34*	0.37*	1.00	0.35**
Overall QoL/health	0.67**	0.63**	0.60**	0.35**	1.00

*p<0.05, **p<0.01

Table 6. Pearson's Correlations between WHOQOL-BREF domains, GHQ-28 sub-scales, and LSI total score for the total sample (N=425).

WHOQOL-BREF Domains	*GHQ-28 Somatic Symptoms*	*GHQ-28 Anxiety/ Insomnia*	*GHQ-28 Social Dysfunction*	*GHQ-28 Severe Depression*	*LSI Total Score*
Physical health	0.62**	0.54**	0.62**	0.46**	0.66**
Mental health	0.56**	0.54**	0.53**	0.51**	0.74**
Social relationships	0.42**	0.38**	0.38**	0.33**	0.76**
Environment	0.11*	0.21**	0.074	0.055	0.35**
Overall QoL/ general health	0.63**	0.55**	0.56**	0.51**	0.70**

*p<0.05, **p<0.01

Convergent validity was further investigated within each of the groups of participants (healthy, psychiatric, physical) producing similar findings (tables 7, 8). In all cases, environment domain demonstrated either no relationship, or mild to moderate correlations with the GHQ-28 sub-scales and the LSI total score. It was also observed that the WHOQOL-BREF social relationships domain accounted for between 62% and 76% of the variance for the LSI total score. This finding supports the validity of social relationships domain consisting of 5 items in the 30-items version, as a good predictor of life satisfaction.

Discriminant validity

The comparison of mean scores between the three groups of participants is shown in table 9. The WHOQOL-BREF discriminated adequately between healthy individuals and patient groups with healthy scoring significantly higher in all four domains, except environment. Differences were also identified between psychiatric patients and physically ill participants, with physically ill achieving higher scores, for all domains with the exception of environment wherein psychiatric patients achieved a slightly higher score.

Test/Re-test reliability

The WHOQOL-BREF was re-administered to healthy participants within 3–4 weeks in order to examine test/retest reliability. The Intraclass Correlation Coefficient (ICC) was applied to the domain scores for both administrations of the instrument. ICC scores in excess of 0.80 were obtained for all domains, demonstrating excellent test-retest reliability (table 10).

Discussion

The present study examines validity and reliability of WHOQOL-BREF 26-items version with the addition of 4 national items. Following WHO guidelines for developing new language versions, focus group participants produced 23 national items, which were subsequently formulated by a panel of researchers to meet the phrasing criteria of WHOQOL items.[30–32] Newly developed items were placed into a separate section of WHOQOL pilot form and were adminis-

Table 7. Pearson's Correlations between WHOQOL-BREF domains, GHQ-28 sub-scales, and LSI total score for healthy participants.

WHOQOL-BREF Domains	*GHQ-28 Somatic Symptoms*	*GHQ-28 Anxiety/ Insomnia*	*GHQ-28 Social Dysfunction*	*GHQ-28 Severe Depression*	*LSI Total Score*
Physical health	0.60**	0.54**	0.45**	0.34*	0.55**
Mental health	0.54**	0.62**	0.35**	0.57**	0.58**
Social relationships	0.28*	0.29*	0.21	0.17	0.70**
Environment	0.17	0.39**	0.12	0.20	0.51**
Overall QoL/ general health	0.49**	0.49**	0.43**	0.42**	0.61**

*p<0.05, **p<0.01

Table 8. Pearson's Correlations between WHOQOL-BREF domains, GHQ-28 sub-scales, and LSI total score for for physically ill (Ph) and psychiatric participants (Ps).

WHOQOL-BREF Domains	*GHQ-28 Somatic Symptoms*		*GHQ-28 Anxiety/ Insomnia*		*GHQ-28 Social Dysfunction*		*GHQ-28 Severe Depression*		*LSI Total*	
	Ph	*PS*	*Ph*	*PS*	*Ph*	*PS*	*Ph*	*PS*	*Ph*	*PS*
Physical health	0.59**	0.59**	0.52**	0.53*	0.55**	0.70**	0.36**	0.67**	0.62**	0.59**
Mental health	0.49**	0.62**	0.50**	0.59*	0.44**	0.69**	0.42**	0.71**	0.57**	0.65**
Social relationships	0.34**	0.51**	0.34**	0.51*	0.30**	0.44**	0.29**	0.47**	0.47**	0.62**
Environment	0.16**	0.21	0.21**	0.27*	0.15*	0.11	0.10	0.33*	0.46**	0.31**
Overall QoL/ general health	0.59**	0.68**	0.54**	0.63*	0.47**	0.66**	0.46**	0.58**	0.44**	0.72**

*p<0.05, **p<0.01, Ph=physical sample, Ps=psychiatric sample, (Note: GHQ-28 scores were reversed)

Table 9. Discriminant validity: Mean score differences between healthy, physically ill and psychiatrically ill participants (ANOVA).

WHOQOL-BREF	*Healthy*	*Physical*	*Psychiatric*	*df*	*F*	*p-value*
Physical health	74.58 (13.40)	63.24 (17.13)	58.06 (17.49)	424	21.32	.000
Mental health	66.79 (12.95)	61.58 (15.68)	53.28 (19.27)	423	17.07	.000
Social relationships	71.49 (13.70)	66.77 (16.77)	54.70 (19.78)	424	27.04	.000
Environment	54.06 (11.69)	57.27 (13.43)	59.23 (13.53)	424	3.34	.036
Overall QoL/ general health	73.69 (16.15)	55.56 (19.75)	52.42 (22.77)	424	27.39	.000

Table 10. Intraclass Correlation Coefficients (ICC) for the healthy sample.

WHOQOL-BREF Domains	*Average measure ICC*
Physical health	.80
Mental health	.87
Social relationships	.87
Environment	.86
Overall QoL/general health	.84

tered to the participants as part of a larger assessment battery.

Next, confirmatory factor analysis (CFA) provided item loadings and indicated objective measures of fit for the WHOQOL-BREF 4-domain model and the fit of new items. The CFA results revealed that the model was fairly good to accommodate the original domain items, while 4 national items loaded signifi-

cantly well on two WHOQOL-BREF domains and were thus included in the Greek version of the instrument producing a 30-item inventory (table 2).

Specifically, 2 new items on nutrition and satisfaction with work were found to load on physical health domain, while other 2 items on home life and social life were found to load onto social relationships domain (Appendix I). The findings appear to reflect values observed within the Greek cultural context giving importance to (a) nutrition with locally produced products; (b) home life with family, partners or alone; (c) social roles performed and acceptance received by others and (d) work including environmental and interpersonal factors. The full content of these facets is presented in a relevant publication on the content of all WHOQOL domains and facets.[42]

These findings are in agreement with international results, proposing national facets or items with similar content in other WHOQOL validation studies. So, in the Taiwan-Chinese versions, two national items were added: one phrased as "being able to get the things you like to eat" loading on the environment domain, and another "having the respect of others" loading on the social relationships domain.[43–44] Also, a facet on eating and appetite has been initially proposed by the Hong Kong WHOQOL centre. In the Chinese-Australian WHOQOL-100, new items were proposed within the existing facets of pain and discomfort, positive feelings, negative feelings and financial resources, while new facets and their items referred to language and literacy and respect and discrimination.[44–45]

Regarding our findings on alpha coefficients, values were very satisfactory supporting internal consistency in all WHOQOL-BREF domains (table 3). We tested the 26-items and the 30-items forms separately and found the latter producing slightly higher alpha scores in the physical health and social relationships domains (tables 3, 4). Thus, we argue that the inclusion of 2 new items within each of the above domains may give strength to domain consistency. Items on nutrition and satisfaction with work seem to add statistical strength and are content consistent with the physical domain. This domain including the level of independence domain items (the original 6 WHOQOL domains merged into 4), has a broader range of items referring to ability to move around, perform work and enjoy various activities. Regarding social relationships domain, inclusion of 2 new items on home life and social life seems to give more power to this domain. The present results support the WHOQOL-BREF 4-domain structure and strengthen particularly social relationships domain, which in several studies restrictions in reliability and validity have been reported.[21]

Further statistical analysis using Pearson's r coefficients produced satisfactory correlations between items and domains and between domain scores. Slightly better values were produced on the 30-items version confirming construct validity of the instrument and supporting further the use of the national version (table 5). Concerning convergent validity, the national version demonstrated goodness to harmonize with other instruments measuring similar concepts, confirming many of the authors' hypotheses. So, physical health and psychological health domains indicated higher correlations with health related sub-scales of GHQ-28 (somatic symptoms and anxiety/insomnia), and social relationships and environment domains with LSI scale

Appendix I. DWHOQOL-BREF: New national items and facets within existing domains.

Domains and facets	*National Items*
Physical health domain	
Facet: Nutrition	1. How healthy and suitable to your needs is the nutrition that you follow?
Facet: Satisfaction with work	2. How much satisfied are you with your job and the employment you have?
Social relationships domain	
Facet: Social life	3. How much satisfied are you with your own social roles and the social activities you are involved with?
Facet: Home life	4. How much satisfied are you with your home life?

including similar content (table 6). Correlations of WHOQOL-BREF with GHQ-28 or LSI were observed in the total sample, as well as in healthy, physical and psychiatric participants (tables 7, 8). Our findings converge with results of several studies providing satisfactory validity of WHOQOL with other associated instruments as i.e. the SF-36, reported in the case of the Brazilian validation study.[46]

Specifically, WHOQOL-BREF physical health and psychological health domains produced –as hypothesized– correlations of moderate to strong values with all four GHQ-28 sub-scales. A milder relationship was identified between WHOQOL-BREF social relationships domain and GHQ-28 sub-scales, supporting the hypothesis of content difference between these measurement tools. The WHOQOL-BREF overall QOL/general health facet demonstrated moderate to strong correlations with all GHQ-28 sub-scales and LSI total score. In addition, as expected, a strong correlation was produced between the WHOQOL-BREF social relationships domain and the total LSI score.

Furthermore, higher correlations were anticipated in the groups of participants with physical or mental disorders. Accordingly, strong correlations were produced between WHOQOL physical health or psychological health domains and the GHQ-28 subscales of social dysfunction and severe depression in the psychiatric participants (table 8).

Application of independent samples t-test and ANOVA investigating the instrument's discriminatory power, verified the assumption that healthy participants would report significantly higher levels of QoL than patient participants. This finding applied to all domains including overall QoL/health facet, with the exception of environment domain (table 9). So, physical health, psychological health and social relationships domains seem to provide higher discriminatory power between groups supporting other international results, e.g. the Polish validation study of the WHOQOL-BREF.[23] It was possible to observe in our study that all groups of participants –healthy, psychiatric, physical– reported relatively lower ratings on the environment domain compared to other domains. Restrictions regarding social services and environmental quality may be suggested to explain this finding. For example, participants from the greater area of Athens reported experiencing low availability and quality of health care, transportation and other facilities. Mean differences between the groups of participants were also observed (table 9) with non-healthy participants reporting relatively higher satisfaction with environment. This finding is in agreement with the Turkish validation study of WHOQOL-BREF arguing that patients of the study might afford a more favorable perspective of their environment because of attention and care provided by health care givers.[47]

Also, discriminatory analysis between patients with physical or mental disorders revealed that physically ill individuals reported higher scores in physical health, psychological health and social relationships domains. It is argued that psychiatric patients in general seem to experience multiple physical, psychological and social deficits, as a result of psychiatric morbidity, leading to poorer ratings in the respective QoL domains. Similar findings were reported in the WHOQOL-100 study.[33] In comparison to healthy individuals, the results of the present study detect reduced QoL in patients with psychiatric or mental disorders and are consistent with previous investigations into self-reported quality of life with similar patient groups, or between subjects with different health conditions.[2–6,9,21]

Concerning sociodemographic variables, participants differed with regard to age and years of education (the healthy subjects being younger and more educated). When the effects of age, education and sex were examined, they were found to be of little influence except the overall QoL/general health facet becoming higher for younger and more educated subjects, and physical health domain for more educated participants. In a study of AIDS pediatric patients in Thailand, sociodemographic factors affecting negatively QoL included age of caregiver (above 45), inadequate financial resources and parental death.[48]

Finally, test-retest reliability was confirmed by Pearson's r and Intraclass Correlation Coefficient (ICC) demonstrating –as expected– that healthy

participants did not report any significant changes in QoL during the time elapsed between administrations of WHOQOL-BREF (table 10).

Improving measurement power of domains

Previous studies indicate that the structure of WHOQOL-BREF with 4 domains and the respective items of facets may reliably measure the concept of QoL in a variety of populations studied.[49] Exception is the Brazilian study not replicating the structure of the original instrument, perhaps because of the population's characteristics, i.e. being working age and relatively healthy.[50]

Most of the studies support the psychometric fitness of physical and psychological health domains, e.g. the Italian WHOQOL-BREF study,[51] while several authors report on the need to strengthen the social relationships domain within the WHOQOL-BREF 4-domain structure.[7,52–54] It is argued that validity of this domain is possibly reduced owing to the limited number of items included.[7,52,53] Accordingly, addition of new items in this domain may provide conceptual power in its assessment, as suggested in the present study.

Regarding the results on environment domain not performing distinctively well as the rest of WHOQOL domains, similar findings have been reported in other studies, referring to restrictions of this domain to discriminate between different patient groups.[47,11] The environment domain may show better discriminatory power with participants experiencing distinct differences in environmental resources or with populations suffering permanent changes in their environmental well-being, i.e. in polluted areas or in physical disasters. This view is supported in the validation study of Bangladesh version showing that environment domain used with adolescent boys, discriminated sufficiently between those living in residential and those of slum areas.[55]

Finally, issues of equivalence between different language versions should not be underestimated in the performance of WHOQOL domains considering that the degree of agreement could be influenced by cultural interpretation of items, facets and domains.[56]

Conclusions

The results of the current study indicate that WHOQOL-BREF Greek version with 4 new items is a valid and reliable tool for measuring QoL in healthy and non-healthy populations. Research and patient-centered use of the instrument can thus be recommended.

Limitations of the study

Investigating psychometric properties, different sampling methodologies can be used including convenience samples besides control selection of participants. In the present study, a non-randomized cross-sectional design, which is common for validation studies, may limit generalizability of findings regarding the specific patient groups, since the selected patients varied i.e. with respect to the stage of the course of illness. QoL profiles of patients with different physical or psychiatric problems are addressed with repeated studies. Also, the reported mean values of groups are considered references to these groups rather than QoL norms.

Authors' contributions

MGC: planning, data collection, analysis, interpretation, preparation, drafting of the manuscript, editing.

ET: data collection, analysis, interpretation, preparation, drafting of the manuscript, editing.

VT: interpretation, editing.

CS: comments on first draft.

VM: interpretation, comments on first draft

GC: comments on first draft, editing.

All authors read and approved the final manuscript

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Ψυχομετρικές ιδιότητες του WHOQOL-BREF σε ομάδες Ελλήνων ασθενών και υγιών ατόμων: Πολιτισμική προσαρμογή με την ενσωμάτωση νέων ερωτήσεων

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Με την παρούσα μελέτη επιδιώκεται ο έλεγχος των ψυχομετρικών ιδιοτήτων της ελληνικής εκδοχής του ερωτηματολογίου WHOQOL-BREF, που αποτελεί τη σύντομη μορφή του ερωτηματολογίου Ποιότητας Ζωής του Παγκόσμιου Οργανισμού Υγείας WHOQOL-100. Η ελληνική εκδοχή περιλαμβάνει τις 26 ερωτήσεις του αγγλικού πρωτοτύπου και 4 επιπλέον ερωτήσεις, που έχουν προκύψει από την προσαρμογή του ερωτηματολογίου (με ομάδες εστιασμένης συζήτησης) στα ελληνικά πολιτισμικά δεδομένα. Η μελέτη του ερωτηματολογίου βασίστηκε σε δείγμα 425 ατόμων, αποτελούμενο από υγιείς και ασθενείς είτε με οργανικές είτε με ψυχιατρικές διαγνώσεις. Με τη μέθοδο της παραγοντικής ανάλυσης, επιβεβαιώθηκε το μοντέλο των τεσσάρων θεματικών ενοτήτων της αγγλικής εκδοχής, στις οποίες εντάσσονται οι 26 ερωτήσεις του πρωτοτύπου. Οι τέσσερεις θεματικές ενότητες και οι αντίστοιχες ερωτήσεις εξετάζουν: (α) τη σωματική υγεία, (β) την ψυχική υγεία, (γ) τις κοινωνικές σχέσεις και (δ) το περιβάλλον. Η παραγοντική ανάλυση ανέδειξε, επίσης, την ένταξη τεσσάρων νέων ερωτήσεων κατάλληλων για την ελληνική εκδοχή του ερωτηματολογίου, ώστε να διαμορφωθεί η ελληνική μορφή των 30 ερωτήσεων. Συγκεκριμένα, 2 ερωτήσεις αναφερόμενες στη διατροφή και στην εργασιακή ικανοποίηση εντάσσονται ικανοποιητικά με στατιστικά κριτήρια στην πρώτη ενότητα της σωματικής υγείας. Οι άλλες δύο ερωτήσεις αναφερόμενες στην κοινωνική ζωή και στην οικογενειακή ζωή ενσωματώνονται ικανοποιητικά στην τρίτη ενότητα των κοινωνικών σχέσεων. Στη συνέχεια, οι στατιστικές αναλύσεις της εσωτερικής συνέπειας εφαρμόστηκαν και στις δύο μορφές του ερωτηματολογίου, των 26 και των 30 λημμάτων, αναδεικνύοντας σχετικά καλύτερα αποτελέσματα για τη μορφή των 30 ερωτήσεων, κυρίως αναφορικά με την τρίτη ενότητα των κοινωνικών σχέσεων. Η ελληνική εκδοχή του ερωτηματολογίου, σύμφωνα με τα αποτελέσματα του ελέγχου των ψυχομετρικών ιδιοτήτων, παρουσιάζει ικανοποιητικά επίπεδα: (α) αξιοπιστίας εσωτερικής συνέπειας, με την τιμή Cronbach's a να κυμαίνεται από 0,67–0,81 (η μορφή των 30 ερωτήσεων περιλαμβάνοντας 4 νέες ερωτήσεις παρουσίασε υψηλότερες τιμές Cronbach's a, με αποτέλεσμα την ενίσχυση των θεματικών ενοτήτων της σωματικής υγείας και των κοινωνικών σχέσεων), (β) εγκυρότητας εννοιολογικής κατασκευής, αναδεικνύοντας ικανοποιητικές συσχετίσεις μεταξύ των ερωτήσεων και των θεματικών ενοτήτων, καθώς και μεταξύ των ερωτήσεων σε κάθε θεματική ενότητα, (γ) συγκλίνουσας εγκυρότητας, καθώς εντοπίζονται σημαντικές συσχετίσεις με το Ερωτηματολόγιο Γενικής Υγείας (GHQ-28) και με την Κλίμακα Ικανοποίησης Ζωής (LSI), (δ) διακριτικής εγκυρότητας, εξασφαλίζοντας την ικανότητα του ερωτηματολογίου να ανιχνεύει διαφορές μεταξύ υγιών και ασθενών και μεταξύ ατόμων με σωματικές νόσους και ασθενών που πάσχουν από ψυχικές διαταραχές και (ε) αξιοπιστίας ελέγχου-επανελέγχου (ICC τιμές για όλες τις θεματικές ενότητες: 0,80–0,87). Η

ελληνική εκδοχή, περιλαμβάνοντας 4 νέες ερωτήσεις που προέκυψαν στο πλαίσιο της πολιτισμικής προσαρμογής του ερωτηματολογίου, αποτελεί ένα αξιόπιστο και έγκυρο εργαλείο εκτίμησης της ποιότητας ζωής, το οποίο μπορεί να χρησιμοποιηθεί στον ευρύτερο χώρο της Υγείας για την αξιολόγηση της ποιότητας ζωής κλινικών ομάδων, αλλά και υγιών ατόμων. Επίσης, αποτελεί κατάλληλο δείκτη αξιολόγησης του θεραπευτικού αποτελέσματος και των παρεχόμενων υπηρεσιών υγείας, αλλά και αξιόπιστο εργαλείο διερεύνησης της ποιότητας ζωής στο πλαίσιο διαπολιτισμικών μελετών.

Λέξεις ευρετηρίου: WHOROL-BREF, εγκυρότητα, αξιοπιστία, ποιότητα ζωής, σωματική νόσος, ψυχική διαταραχή.

References

1. Hofer A, Kemmler G, Eder U, Edlinger M, Hummer M, Fleischhacker WW. Quality of life in schizophrenia: the impact of psychopathology, attitude toward medication, and side effects. *J Clin Psychiat* 2004, 65:932–939
2. Goldney RD, Fisher LJ, Wilson DH, Cheok FC. Major depression and its associated morbidity and quality of life in a random, representative Australian community sample. *Aust NZ J Psychiat* 2000, 34:1022–1029
3. Saarijarvi S, Salminen JK, Toikka T, Raitasalo R. Health-related quality of life among patients with major depression. *Nord J Psychiat* 2002, 56:261–264
4. Rudolf H, Priebe S. Subjective quality of life and depressive symptoms in women with alcoholism during detoxification treatment. *Drug Alcohol Depend* 2002, 66:71–76
5. Holzner B, Kemmler G, Sperner-Unterweger B, Kopp M, Dunser M, Margreiter R et al. Quality of life measurement in oncology-a matter of the assessment instrument? *Eur J Cancer* 2001, 37:2349–2356
6. Erickson S, Williams B, Gruppen L. Relationship between symptoms and health related quality of life in patients treated for hypertension. *Pharmacotherapy* 2004, 24:344–350
7. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. *Qual Life Res* 2000, 9:121–124
8. Skevington SM. Advancing cross-cultural research on quality of life. Observations drawn from the WHOQOL development. *Qual Life Res* 2002, 11:135–144
9. Power M, Harper A, Bullinger M. The World Health Organization WHOQOL-100: tests of the universality of Quality of Life in 15 different cultural groups worldwide. *Health Psychol* 1999, 18:495–505
10. Saxena S, Carlson D, Billington R, Orley J (on behalf of the WHOQOL Group). The WHO quality of life assessment instrument (WHOQOL-Bref): The importance of its items for cross-cultural research. *Qual Life Res* 2001, 10:711–721
11. WHOQOL Group. The World Health Organization quality of life assessment (WHOQOL). Development and general psychometric properties. *Soc Sci Med* 1998, 46:1569–1585
12. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004, 13:299–310
13. Skevington SM, Mac Arthur P, Somerset M. Developing items for the WHOQOL: An investigation of contemporary beliefs about quality of life related to health in Britain. *Br J Health Psychol* 1997, 2:55–72
14. Skevington SM, Bradshaw J, Saxena S. Selecting national items for the WHOQOL: Conceptual and psychometric considerations. *Soc Sci Med* 1999, 48:473–487
15. Bonicatto S, Serial JJ, Seguezzo M. WHOQOL-BREF: Some Psychometric Considerations of the Argentine Version. Paper presented at the 4th Annual Conference of the ISOQOL, 4–9 November 1997, Vienna, Austria
16. Saxena S, Chandiramani K, Bhargava R. WHOQOL-Hindi: A questionnaire for assessing quality of life in health care settings in India. *Natl Med J India* 1998, 11:160–165
17. Mahatnirunkul S, Tuntipiwatanaskul W, Poompisanchai W. Comparison of the WHOQOL-100 and the WHOQOL-BREF. *J Ment Hth Thailand* 1998, 5:4–15
18. Hawthorne G, Richardson J, Day N, McNeil H. *Validation of the WHOQOL-BREF*. Centre for Health Program Evaluation, Melbourne, Australia, 2000
19. Eser E, Fidaner H, Fidaner C, Eser SY, Elbi H, Goker E: WHOQOL-BREF: a suitable instrument for the assessment of quality of life for use in the health care settings in Turkey. *Qual Life Res* 1999, 8:647
20. Norholm V, Bech P. The WHO Quality of Life (WHOQOL) Questionnaire: Danish validation study. *Nord J Psychiat* 2001, 55:229–235
21. Min SK, Kim KI, Lee CI, Jung YC, Suh SY, Kim DK. Development of the Korean versions of WHO Quality of Life scale and WHOQOL-BREF. *Qual Life Res* 2002, 11:593–600
22. Hasanah CI, Naing L, Rahman AR. World Health Organization Quality of Life Assessment: brief version in Bahasa Malaysia. *Med J Malaysia* 2003, 58: 79–88
23. Jaracz K, Kalfoss M, Górna K, Baczyk G. Quality of Life in Polish respondents: psychometric properties of the Polish WHOQOL-Bref. *Scand J Caring Sci* 2006, 20: 251–260
24. Umansky R, Amir M, Fridmann M, Zidon E, Chen D, Nemetz B. Was it a good move? Improvement in quality of life among chronic mental patients moving from a mental hospital to a hostel in the community. *Israel J Psychiat* 2003, 40:248–57
25. Hwang HF, Liang WM, Chiu YN, Lin MR. Suitability of the WHOQOL-BREF for community-dwelling older people in Taiwan. *Age Ageing* 2003, 32:593–600
26. Chan GW, Ungvari GS, Shek DT, Leung Dagger JJ. Hospital and community-based care for patients with chronic schizophrenia in Hong Kong-quality of life and its correlates. *Soc Psych Psych Epid* 2003, 38:196–203

27. Chandra PS, Deepthivarma S, Jairam KR, Thomas T. Relationship of psychological morbidity and quality of life to illness-related disclosure among HIV-infected persons. *J Psychosom Res* 2003, 54:199–203
28. Mooney M, Hannon F, Barry M, Friel S, Kelleher C. Perceived quality of life and mental health status of Irish female prisoners. *Irish Med J* 2002, 95:241–243
29. Kalfoss M, Isaksen AS, Thuen F, Alve S. The Suitability of the World Health Organisation Quality of Life Instrument-BREF in Cancer Relatives. *Cancer Nurs* 2008, 31:11–22
30. Ginieri-Coccossis M, Antonopoulou V, Triantafillou E, Christodoulou GN. Translation and Cross-Cultural Adaptation of WHOQOL-100 in Greece: Part I. *Psychiatry Today* 2001, 32:5–16
31. Ginieri-Coccossis M, Triantafillou E, Antonopoulou V, Christodoulou GN. Translation and Cross-Cultural Adaptation of WHOQOL-100 in Greece: Part II. *Psychiatry Today* 2001, 32:27–40
32. World Health Organization. MNH/PSF95.2.Rev.1. *Resources for New Centres*. WHO, Geneva, 1996
33. Ginieri-Coccossis M, Liappas IA, Tzavellas E, Triantafyllou E, Soldatos C. Detecting changes in quality of life and psychiatric symptomatology following an in-patient detoxification programme for alcohol-dependent individuals: The use of WHOQOL-100. *Int J Exper Clin Pathopsys Drug Res* 2007, 21:99–106
34. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. DC: American Psychiatric Association, Washington, 1994
35. WHOQOL Group. Development of the WHOQOL-BREF Quality of Life Assessment. *Psychol Med* 1999, 28:551–558
36. Ginieri-Coccossis M, Triantafillou E, Tomaras V, Liappas IA, Christodoulou GN, Papadimitriou GN. Quality of life in mentally ill, physically ill and healthy individuals: The validation of the Greek version of the World Health Organization Quality of Life (WHOQOL-100) questionnaire. *Ann Gen Psych* 2009, 8:23 doi:10.1186/1744-859X-8-23
37. Fountoulakis K, Iakovides B, Iakovides A, Christofides A, Ierodiakonou C. The validation of the Life Satisfaction Inventory (LSI) in the Greek population. *Psychiatriki* (in Greek) 1997, 8:292–304
38. Muthny FA, Koch U, Stump S. Quality of life in oncology patients. *Psychother Psychosom* 1990, 54:145–160
39. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psycholog Med* 1979, 9:139–140
40. Garyfallos G, Karastergiou A, Adamopoulou A, Moutzoukis C, Alagiozidou E, Mala D et al. A Greek version of the General Health Questionnaire: Accuracy of translation and validity. *Acta Psychiat Scand* 1991, 84:371–378
41. Bryman A, Cramer D. *Quantitative Data Analysis*. Routledge, London, New York, 1997
42. Ginieri-Coccossis M, Triantafillou E, Antonopoulou V, Tomaras V, Christodoulou GN. *WHOQOL Manual for Facets and Domains*. Beta Medical Publ, Athens, 2003, 2009 (in Greek)
43. Yao G, Chung CW, Yu CF, Wang JD. Development and verification of validity and reliability of the WHOQOL-BREF Taiwan version. *J Formos Med Assoc* 2002, 101:342–51
44. Leung KF, Wong WW, Tay MSM, Chu MML, Ng SSW. Development and validation of the interview version of the Hong Kong Chinese WHOQOL-BREF. *Qual Life Res* 2005, 14:1413–1419
45. Murphy B, Herrman H, Hawthorne G, Pinzone T, Evert H. *Australian WHOQOL instruments: User's manual and interpretation guide*. Australian WHOQOL Field Study Centre, Melbourne, Australia, 2000
46. Barros da Silva Lima AF, Fleck M, Pechansky F, de Boni R, Sukop P. Psychometric properties of the World Health Organization Quality of Life instrument (WHOQOL-BREF) in alcoholic males: A pilot study. *Qual Life Res* 2005, 14:473–478
47. Dündar P, Fidaner H, Oral A, Eser S, Atman UC, Pala T. Comparing the Turkish versions of WHOQOL-BREF and SF-36. Convergent validity of WHOQOL-BREF and SF-36. *Hippokratia* 2002, 6:37–43
48. Kuntawee C, Fungladda W, Kaewkungwal J, Chanthavanich P, Chotpittayasunon T. Social factors related to quality of life among HIV infected children in ubon Ratchathani Province, Thailand. *Southeast Asian J Trop Med Public Heal* 2010, 41:1136–1144
49. Trompenaars FJ, Masthoff ED, Van Heck GL, Hodiamont PP, De Vries J. Content validity, construct validity and reliability of the WHOQOL-BREF in a population of Dutch adult psychiatric outpatients. *Qual Life Res* 2005, 14:151–160
50. Moreno AB, Faerstein E, Werneck GL, Lopes CS, Chor D. Psychometric Properties of the World Health Organization Abbreviated Instrument for Quality of Life Assessment in the Pro-Saude Study. *Cad Saúde Pública* 2006, 22:2585–2597
51. De Girolamo G, Rica P, Scocco P, Becchi A, Coppa F, D' Addario A et al. Quality of life assessment: validation of the Italian version of the WHOQOL-Brief. *Epidemiol Psychiatr Soc* 2000, 9: 45–55
52. Naumann VJ, Byrne GJ. WHOQOL-BREF as a measure of quality of life in older patients with depression. *Int Psychogeriatr* 2004, 16:159–173
53. Taylor WJ, Myers J, Simpson RT, McPherson KM, Weatherall M. Quality of life of people with rheumatoid arthritis as measured by the World Health Organization Quality of Life Instrument, short form (WHOQOL-BREF): score distributions and psychometric properties. *Arthritis Rheum* 2004, 51:350–357
54. Paskulin LG, Molzahn A: Quality of life of older adults in Canada and Brazil. *West J Nurs Res* 2007, 29:10–26. doi: 10.1177/0193945906292255O
55. Izutsu T, Tsutsumi A, Islam A, Matsuo Y, Yamada HS, Kurita H et al. Validity and reliability of the Bangla version of WHOQOL-BREF on an adolescent population in Bangladesh. *Qual Life Res* 2005, 14:1783–1789
56. Chien CW, Wang JD, Yao G, Hsueh IP, Hsieh CL. Agreement between the WHOQOL-BREF Chinese and Taiwanese versions in the elderly. *J Formos Med Assoc* 2009, 108:164–169

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Research article
Ερευνητική εργασία

Low dosage lithium augmentation in venlafaxine resistant depression: An open-label study

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Lithium augmentation is one of the best studied strategies for resistant depression. The lithium dosage usually given is around 900 mg/day and plasma level is maintained in the range of 0.5–0.8 mEq/L. However, the administration of lithium in this dosage necessitates monitoring of plasma concentration and increases the risk of toxicity and side effects. Since it has been shown that low lithium levels increase serotonin turnover and enhance serotonin neurotransmission, we thought it of interest to assess the efficacy of low dosage lithium augmentation for patients with resistant depression. Fifty one patients suffering from severe unipolar or bipolar depression who had failed to respond to treatment with venlafaxine 300–375 mg/day were included in the study and treated as outpatients. Patients had previously been exposed to unsuccessful treatment with various antidepressants, mostly SSRIs. After a washout period for previously administered antidepressants of one week, the dosage of venlafaxine was rapidly titrated to 300 or 375 mg/day, corresponding to about 5 mg/kg. The dose remained stable during the next six weeks. Additional antipsychotic medication was allowed to treat psychotic symptoms. Forty seven severely depressed patients who failed to respond to 300–375 mg/day venlafaxine were, in addition, given lithium carbonate in low dosage (300–450 mg/day). The Clinical Global Impression Improvement scale was used as the treatment outcome. A score of 1 or 2 was considered as non-response. All patients gave informed consent to participate in the study. Ratings were performed at baseline and after 1,2 and 5 weeks. Lithium plasma concentration measurements were performed after 1 and 4 weeks. After 5 weeks of augmentation, 51% of the patients were rated as "much" or "very much" improved. Bipolar patients showed a better response than unipolar (64.3% *vs* 45.5%, $p<0.038$). Most patients (76%) showed a rapid response (up tp 7 days), and only 2 patients (4.6%) responded after more than 2 weeks The mean lithium plasma level was 0.33±0.09 mEq/L. No significant differences were found in treatment response with regard

to sex, family history, psychotic symptomatology and suicidal ideation. No troublesome side effects were reported. Our results show that treatment augmentation with low lithium dosage may be as effective as augmentation with higher dosage, is well tolerated and does not necessitate monitoring of plasma level. Hence, an initial trial of augmentation at low dosage lithium may be the preferred first choice in non-emergent situations. The low dosage also minimizes the risk of side effects and drug-drug interactions. Prospective controlled studies to confirm our findings are needed as are larger scale comparisons with therapeutic dose lithium augmentation.

Key words: Resistant depression, severe depression, venlafaxine, lithium augmentation.

Introduction

Many case reports, open trials, placebo-controlled studies, reviews and meta-analyses of these studies concluded that, there is significant evidence to support the efficacy and utility of lithium augmentation.[1–4] Lithium may cause severe adverse effects[5] and increases the risk of toxicity,[6] but is well tolerated when lower doses are used. Moreover, lithium administration necessitates careful monitoring of plasma concentration and also requires multiple daily dosing. For these reasons, although lithium augmentation is the treatment option of first choice in refractory depression, it has lost popularity and is not widely used. It is a common practice to maintain serum lithium concentrations in the range of 0.5 to 0.8 mmol/L. However, some studies have shown that low lithium dosage may be beneficial as augmentation strategy with plasma level ranging between 0.15 and 0.40 mEq/L.[7–9] The present study was designed to evaluate the efficacy of low lithium dosage augmentation in venlafaxine resistant patients. With low dosage, troublesome adverse effects, toxicity and possible drug-drug interactions are avoided and treatment compliance may be enhanced.

Material and method

Fifty one patients suffering from severe unipolar or bipolar depression who had failed to respond to treatment with venlafaxine 300–375 mg/day were included in the study and treated as outpatients. Patients had previously been exposed to unsuccessful treatment with various antidepressants, mostly SSRIs. After a washout period for previously administered antidepressants of 1 week, the dosage of venlafaxine was rapidly titrated to 300 or 375 mg/day, corresponding to about 5 mg/kg. The dose remained stable during the next 6 weeks. Patients who did not respond were administered lithium carbonate at a single evening dose as low as 300–450 mg/day and this was continued for 5 weeks. Additional antipsychotic medication was allowed to treat psychotic symptoms. The severity of depressive episode was assessed using the Clinical Global Impression-Severity of Illness (CGI-S).[10] The Clinical Global Impression- Improvement Scale (CG-I) (7-points) was used as the main outcome measure. A score of 1 or 2 was considered as non-response. All patients gave informed consent to participate in the study. Ratings were performed at baseline and after 1.2 and 5 weeks. Lithium plasma concentration measurements were performed after 1 and 4 weeks. Vital signs, blood pressure and unwanted effects were recorded at each visit. Differences in demographic and clinical variables between groups were analyzed by independent t-tests or x^2 tests. The changes from baseline in CGI scores were analyzed with paired t-tests.

Results

Forty seven patients (30 women, 17 men) received lithium augmentation and were included for analysis. Thirty three were diagnosed with unipolar depression and 14 with bipolar affective disorder, currently depressed, according to DSM-IV criteria. Nineteen patients suffered from psychotic major depression. Twenty (44.7%) had suicidal ideation

and 8 (17%) had a history of attempted suicide in the current episode. Four patients discontinued during the augmentation period. Table 1 summarizes the demographic and clinical characteristics of patients, lithium dosage and plasma level. The mean lithium dosage was 353.3±85.5 mg/day and the mean plasma concentration 0.33±0.09 mmoL/L. Five patients (10.6%) scored 7 (very severely ill) in CGI-S scale, 34 patients (72.3%) scored 6 (severely ill) and 8 patients (17.0%) scored 5 (markedly ill). The mean CGI-S score decreased from 5.91±0.62 at baseline to 3.49 (±...) at the end of 5th week (t=11.2, p-0,000). Twenty four patients (51%) scored 1 or 2 "very much" or "much improved" in CGI-I scale, and 23 patients (49%) scored at least 3 at week 5. Bipolar patients showed a better response than unipolar (64.3% *vs* 45.5%, x^2=6.87, p<0.038). Four bipolar patients (28.6%) recovered in comparison with 1 unipolar (3.0%) (x^2=4.68, p<0.03). Most patients (76%) showed a rapid response (up to 7 days), and only 2 patients (4.6%) responded after more than 2 weeks. None of the bipolar patients switched to mania or hypomania during the treatment period. No significant differences were found in treatment response with regard to sex, family history, psychotic symptomatology and suicidal ideation. The most common adverse effects with venlafaxine were nausea, sweating and headache. No additional adverse effects were reported with venlafaxine plus lithium.

Table 1. Study patients profile

No of patients	47
Sex (male: female)	17:30
Age (y)-(Range)	43.6±16.3 (20–69)
Diagnosis N(%)	
Unipolar	33 (70.2)
Bipolar I	6 (12.8)
Bipolar II	8 (17.0)
With psychotic symptoms	19 (40.4)
Without psychotic symptoms	28 (59.6)
Lithium dosage (mg)	353.3±85.5
Lithium plasma level	0.33±0.09
CGI Severity score	5.91±0.62
Mean venlafaxine dose (mg)	305 (300–375)

Discussion

Of our patients (N=47), 51% obtained a positive response and 72.3% had at least a partial response. This response rate was higher than that of Hpencamp et al[11] and Bertschy et al[11] who found a 35% and a 38.4% response respectively in venlafaxine-resistant patients treated with lithium augmentation. Mean lithium plasma levels in these studies were 0.66±0.19 mEq/L and 0.81±0.22 mEq/L, respectively. The overall 51% response rate in this study is similar to that reported in previous studies 2–3 where higher lithium dosage was used. We also found a 10.6% rate of complete remission in comparison with 9% of the study of Hoencamp et al[11] and 23% of the study of Bertschy et al.[12] No patient withdrew for adverse effects due probably to the low dosage of lithium. All patients were severely depressed and had failed to respond to previous trials with various antidepressants. A better response to lithium augmentation of patients with more severe depression was found by Bschor et al,[13] who found that severity of depression was a predictor of response to lithium augmentation.

The low lithium dosage we used was well tolerated and the venlafaxine-lithium combination did not cause additional adverse affects other than those caused by venlafaxine. Patients with rapid and dramatic response (5) had lower, but not statistically significant plasma level (0.3 *vs* 0.4 mEq/L). Similarly, Thase et al[4] found lower plasma level in patients who showed a rapid (within 3 days) and complete recovery. Bipolar patients responded better than unipolar patients to lithium augmentation (p<0.03). The results in the literature are contradictory. Similarly to Rybakowski and Matkowski[14] we found a better response when improvement occured during the first week than later.

Our results show that plasma lithium levels above 0.5 mEq/L are not necessary to obtain treatment response in refractory depressive patients. This is consistent with several studies showing a good response with low lithium levels. Kushnir et al[7] reported a 100% response rate with plasma levels ranging

between 0.15 mEq/L and 0.40 mEq/L in a geriatric population. Fava et al[8] reported that lithium augmentation of fluoxetine (20–40 mg/day) was effective with dosage 300–600 mg/day and plasma 0 levels 21±0.11 mEq/L.

Lithium acts through multiple pathways to inhibit glycogen synthetase kinase-3 beta (GSK3 beta). This enzyme phosphorylates and inhibits nuclear factors that turn on cell growth and protection programs, including the nuclear factor of activated T cells (NFAT) and WNT/beta-catenin. In animals, lithium upregulates neurotrophins, including brain-derived neurotrophic factor (BDNF), nerve growth factor, neurotrophin-3 (NT3), as well as receptors to these growth factors in brain. Lithium also stimulates proliferation of stem cells, including bone marrow and neural stem cells in the subventricular zone, striatum, and forebrain. The stimulation of endogenous neural stem cells may explain why lithium increases brain cell density and volume in patients with bipolar disorders. Lithium also increases brain concentrations of the neuronal markers n-acetyl-aspartate and myoinositol. Lithium also remarkably protects neurons against glutamate, seizures, and apoptosis due to a wide variety of neurotoxins.[15]

It has been proposed that in depression lithium augmentation may promote improvement via an increase of central serotonergic function.[14] This may indicate that low dose lithium may further increase serotonergic function to produce a therapeutic effect, while higher doses may cause adverse effects via serotonergic stimulation. It has been shown that low plasma levels of lithium (0.1 mEq/L) increase the turnover of serotonin neurons and enhance serotonergic neurotransmission.[16]

Our results indicate that low dosage lithium augmentation is an effective and well tolerated treatment for the more severely depressed patients who are refractory to venlafaxine with a response rate of at least 50% after a period of 2–3 weeks. The low dosage makes the lithium-antidepressant combination safe, user friendly, not necessitating monitoring of plasma lithium concentration and practically without risk of toxicity and drug interactions. Prospective controlled studies to confirm our findings are needed.[17] In addition larger scale studies comparing therapeutic to subtherapeutic lithium augmentation or perhaps sequential treatment, initially with subtherapeutic and then with therapeutic does in bipolar versus unipolar non-responders would be useful for algorithm treatment of depression.

Ενίσχυση με χαμηλή δόση λιθίου της αγωγής με βενλαφαξίνη στην ανθεκτική κατάθλιψη: Μια ανοιχτή μελέτη

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Η ενίσχυση της αντικαταθλιπτικής αγωγής με λίθιο είναι μία από τις καλύτερα μελετημένα στρατηγικές για την ανθεκτική κατάθλιψη. Η δοσολογία λιθίου συνήθως είναι περίπου 900 mg/ημέρα και το επίπεδο του πλάσματος διατηρείται στην περιοχή του 0,5–0,8 mEq/L. Ωστόσο, η χορήγηση του λιθίου σε αυτή τη δοσολογία απαιτεί την παρακολούθηση της συγκέντρω-

σης στο πλάσμα και αυξάνει τον κίνδυνο της τοξικότητας και άλλων ανεπιθύμητων ενεργειών. Δεδομένου ότι έχει αποδειχθεί ότι τα χαμηλά επίπεδα του λιθίου αυξάνουν την ανακύκλωση της σεροτονίνης και την ενίσχυση της νευροδιαβίβασης με σεροτονίνη, σκεφτήκαμε ότι παρουσιάζει ενδιαφέρον για την αξιολόγηση της αποτελεσματικότητας της ενίσχυσης με χαμηλή δοσολογία λιθίου για ασθενείς με ανθεκτική κατάθλιψη. Πενήντα ένας ασθενείς που έπασχαν από σοβαρή μονοπολική ή διπολική κατάθλιψη και που δεν ανταποκρίθηκαν στη θεραπεία με βενλαφαξίνη 300–375 mg την ημέρα συμπεριελήφθησαν στη μελέτη ως εξωτερικοί ασθενείς. Οι ασθενείς είχαν προηγουμένως εκτεθεί σε ανεπιτυχή θεραπεία με διάφορα αντικαταθλιπτικά, ως επί το πλείστον SSRI. Μετά από μια περίοδο έκπλυσης μίας εβδομάδας για προηγουμένως χορηγηθέντα αντικαταθλιπτικά, η δόση της βενλαφαξίνης ταχέως τιτλοποιήθηκε σε 300 ή 375 mg/ημέρα, δόση που αντιστοιχεί σε περίπου 5 mg/kg. Η δόση παρέμεινε σταθερή κατά τη διάρκεια των επόμενων έξι εβδομάδων. Πρόσθετα αντιψυχωσικά φάρμακα επιτρεπόταν να χορηγηθούν για τη θεραπεία των ψυχωσικών συμπτωμάτων. Σε 47 σοβαρά καταθλιπτικούς ασθενείς οι οποίοι απέτυχαν να ανταποκριθούν σε 300–375 mg/ημέρα βενλαφαξίνης χορηγήθηκε στη συνέχεια ανθρακικό λίθιο σε χαμηλές δόσεις (300–450 mg/ημέρα). Η CGI χρησιμοποιήθηκε για να αξιολογήσει το αποτέλεσμα της θεραπείας. Ο βαθμός 1 ή 2 θεωρήθηκε ως μη απάντηση. Όλοι οι ασθενείς έδωσαν συγκατάθεση για τη συμμετοχή στη μελέτη. Βαθμολογήσεις πραγματοποιήθηκαν κατά την έναρξη και μετά από 1, 2 και 5 εβδομάδες. Μετρήσεις της συγκέντρωσης του λιθίου πλάσματος έγιναν μετά από 1 και 4 εβδομάδες. Μετά από 5 εβδομάδες, το 51% των ασθενών βελτιώθηκε «πολύ» ή «πάρα πολύ». Διπολικοί ασθενείς ανταποκρίθηκαν καλύτερα από τους μονοπολικούς. Το μέσο επίπεδο του λιθίου στο πλάσμα ήταν 0,33±0,09 mEq/L. Δεν βρέθηκαν σημαντικές διαφορές στην ανταπόκριση στη θεραπεία σε σχέση με το φύλο, το οικογενειακό ιστορικό, την ψυχωτική συμπτωματολογία και τον αυτοκτονικό ιδεασμό. Δεν αναφέρθηκαν σημαντικές ανεπιθύμητες ενέργειες. Τα αποτελέσματά μας δείχνουν ότι η ενίσχυση της θεραπείας με χαμηλή δόση λιθίου μπορεί να είναι εξίσου αποτελεσματική με την ενίσχυση με μεγαλύτερη δοσολογία. Η χαμηλής δόσης ενίσχυση είναι καλά ανεκτή και δεν απαιτεί παρακολούθηση των επιπέδων πλάσματος. Ως εκ τούτου, μια πρώτη δοκιμή της αύξησης σε χαμηλές λιθίου δόση μπορεί να είναι η προτιμώμενη πρώτη επιλογή σε μη ανταποκρινόμενες καταθλίψεις. Η χαμηλή δοσολογία ελαχιστοποιεί τον κίνδυνο ανεπιθύμητων ενεργειών και αλληλεπιδράσεων μεταξύ φαρμάκων. Χρειάζονται μελέτες με ομάδες ελέγχου για να επιβεβαιώσουν τα ευρήματά μας, καθώς και μεγαλύτερα δείγματα ασθενών με εν συνεχεία αύξηση της δόσης του λιθίου στους μη ανταποκρινόμενους στη χαμηλή δόση ασθενείς.

Λέξεις ευρετηρίου: Ανθεκτική κατάθλιψη, σοβαρή κατάθλιψη, βενλαφαξίνη, ενίσχυση με λίθιο.

References

1. Cipriani A, Barbui C, Butler R, Hatcher S, Geddes J Depression in adults: drug and physical treatments. *Clin Evid* (Online) 2011, pii:1003
2. Rouillon F, Gorwood P. The use of lithium to augment antidepressant medication. *J Clin Psychiatry* 1998, 59(Suppl 5):32–39
3. Bauer M, Forsthoff A, Baethge C, Adli M, Berghöfer A, Döpfmer S et al. Lithium augmentation therrapy in refractory depression: update 2002. *Eur Arch Psychiat Clin Neurosci* 2003, 253: 132–139
4. Thase ME, Kupfer DJ, Frank E. Treatment of imipramine-resistant recurrent depression, II: an open clinical trial of lithium augmentation. *J Clin Psychiatry* 1989, 50:413–417
5. Van Marwijk HW, Bekker FM, Nolen WA, Jansen PA, van Nieuwkerk JF et al. Lithium augmentation in geriatric depression. *J Affect Disord* 1990, 20:217–223
6. Austin LS, Arana GW, Melvin JA. Toxicity resulting from lithium augmentation of antidepressant treatment in elderly patients. *J Clin Psychiatry* 1990, 51:344–345
7. Kushnir SL, Lithium antidepressant combinations in the treatment of depressed, physically ill geriatric patients. *Am J Psychiatry* 1986, 43:378–379
8. Dinan TG. Lithium augmentation in sertraline-resistant depression: A preliminary dose-response study. *Acta Psychiatr Scand* 1993, 88:300–301

9. Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: A double-blind, controlled study. *Am J Psychiatry* 1994, 151:1372–1374
10. Guy W (ed) ECDEU. *Assessment Manual for Psychopharmacology*, Publication ADM 76-338, Rockville, MD Department of Health, Education and Welfare, 1976:217–222
11. Hoencamp E, Haffmans J, Dijken WA, Huijbrechts IP. Lithium augmentation of venlafaxine: An open-label trial. *J Clin Psychopharmacol* 2000, 20:538–543
12. Bertschy G, Ragama-Pardos E, Aot-Ameur A, Muscionico M, Favre S, Roth L. Lithium augmentation in venlafaxine nonresponders: an open study. *Eur Psychiatry* 2003, 18:314–317
13. Bschor T, Canata B, Müller-Oerlinghausen B, Bauer M. Predictors of response to lithium augmentation in tricyclic antidepressant resistant depression. *J Affect Disorder* 2001, 64:261–265
14. Rybakowski J, Matkowski K. Adding lithium to antidepressant therapy: factors related to therapeutic potentiation. *Eur Neuropsychopharmacol* 1992, 2:161–165
15. Young W. Review of lithium effects on brain and blood. *Cell Transplant* 2009, 18:951–975
16. McCance-Katz E, Price LH, Charney PS, Herninger G. Serotonergic function during lithium augmentation of refractory depression. *Psychopharmacology* 1992, 108:93–97
17. Blier P, De Montigny C. Short term lithium administration enhances serotonergic neurotransmission: electrophysiologic evidence in rat CNS. *Eur J Pharmacol* 1985, 113:69–77

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Research article
Ερευνητική εργασία

Alexithymia, depression and serum lipids in suicide attempters

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Over the last decade several studies have discussed the association between serum cholesterol, depressive disorders and suicide. A specific psychological variable related to affect is alexithymia. Alexithymia has been linked to depression and suicidal behaviour. Concerning lipid levels there are several studies that suggest changes in serum lipid composition maybe related to depression and suicidal behaviour. In this study we examined the possible relationship between alexithymia, depression and serum lipids in suicide attempters. We studied 50 non-violent suicide attempters (drug overdosers) with a mean age of 35.0 (±12.2) years. Alexithymia was measured using the Shalling-Sifneos Personality Scale Revised (SSPS-R) and depression using the Montgomery-Asberg Depression Rating Scale (MADRS). Serum lipids concentrations were determined by enzymatic method within 24h of hospital admission. For the statistical evaluation Spearman's rank correlation coefficients were used. The mean serum lipid levels were: total serum cholesterol (TC) 175.2 (±29.6) mg/dL, high-density lipoprotein cholesterol (H-DLC) 47.08 (±13.1) mg/dL, low density lipoprotein cholesterol (L-DLC) 109.5 (±23.5) mg/dL and the mean serum triglycerides (TR) level was 89.4 (±39.1) mg/dL. The mean scores on the questionnaires were: SSPS-R 10.3 (±3.7), MADRS 33.5 (±5.9). There were significant correlations between: (a) SSPS-R score and MADRS score ($r=0.439$, $p<0.001$), (b) SSPS-R score and TR level ($r=0.323$, $p<0.05$). There were no significant correlations between MADRS score and any of the lipid fractions measured. To our knowledge, only few studies have examined the association between alexithymia and clinical-psychopathological parameters in suicide attempters. There are no previous studies comparing serum lipid profile with alexithymia in suicide attempters. This is the first study to compare at the same time serum lipids, alexithymia and depression in suicide attempters. The results suggest that although there was a strong relationship between alexithymia and depression in suicide attempters only alexithymia was correlated to Serum triglyceride levels.

Key words: Alexithymia, depression, serum lipids, suicide attempt, drug overdose.

Introduction

The term "alexithymia" was introduced in 1972 by Peter Sifneos.[1] It has originated from the Greek words a=lack, lexis=word, and thymos=feeling. Alexithymia (AL) is considered to be a difficulty in the awareness of one's feelings and/or a difficulty of finding words to describe one's own feelings.[2,3] Subjects with alexithymia fail to express their feelings, avoid interpersonal conflicts and display more negative affects. Alexithymia is not unique to depression, but is seen in about to 45% of patients with depression. Its presence in major depression has also been linked to severity of depression and suicide risk.[4–6] Some studies have suggested an association of low cholesterol levels with increased morbidity of depression and/or suicidal behaviour.[7–9] However, recent research findings are inconsistent, thus, increases, decreases or no change in serum lipid levels have been reported in patients with depression and/or suicide attempts.[10,11] The aim of this study is to examine possible relationships between alexithymia, depression and serum lipids in a group of non-violent suicide attempters.

Material and method

Fifty suicide attempters by drug overdose (non-violent way) consecutively admitted to Pathology Department, Red Cross General Hospital, Athens were included in the study. There were 68% women and 32% men with a mean age of 35.0 (±12.2) years. All attempters provided informed consent after receiving a full explanation of the study. Information regarding demographic data, past psychiatric and medical history, medication used, alcohol intake, intoxication at the time of suicide attempt, body weight and height as well as history of suicide attempts were collected using a semi-structured interview schedule. Attempters less than 18-years old or more 59-years old, subjects with current infection or serious medical illness, female attempters on contraceptives, patients with eating disorders or drug abuse were excluded. Subjects were free of drugs known to affect lipid levels. All subjects had normal blood tests including haematological, renal, liver and thyroid function tests. Blood sample was drawn by venipuncture the day after the suicide attempt at 8 a.m. Serum lipid concentrations were determined by enzymatic methods. All attempters were assessed concomitantly using the Schalling-Sifneos Personality Scale Revised (SSPS-R)[12] and the Montgomery-Asberg Depression Rating Scale (MADRS)[13] by the same psychiatrist-rater. Data were analyzed using the SPSS software for windows (version 8.0). For the statistical evaluation Sperman's rank correlation coefficients were used.

Results

The mean total serum cholesterol (TC) level of the attempters was 175.2 (±29.6) mg/dL, the mean high-density lipoprotein cholesterol (H-DLC) level was 47.08 (±13.1) mg/dL, the mean low density lipoprotein cholesterol (L-DLC) level was 109.5 (±23.5) mg/dL and the mean serum triglycerides (TR) level was 89.4 (±39.1) mg/dL. The mean SSPS-R score was 10.3 (±3.7) and the mean MADRS score was 33.5 (±5.9). We found significant correlations between SSPS-R score and MADRS score ($r=0.439$, $p<0.001$) as well as between SSPS-R score and TR level ($r=0.323$, $p<0.05$). There were no significant correlations between MADRS score and any of the lipid fractions measured (table 1).

Discussion

During the past decades several epidemiological studies have described an association between lower cholesterol concentrations and increased suicide risk.[14,15] However, recent clinical studies concerning cholesterol levels in depressed patients with or without suicidal behaviour had contradictory results,[7–11,16,17] To our knowledge, there are few studies on the association between AL and clinical-psychopathological parameters in suicide attempters[18–20] and there are no

Table 1. Intercorrelations between SSPS-R score, MADRS score and serum lipid levels

	MADRS	TC	H-DLC	L-DLC	TR
SSPS-R	r=0.439 p<0.001	r=0.195 NS	r=0.096 NS	r=0.275 NS	r=0.323 p<0.05
MADRS		r=0.192 NS	r=0.076 NS	r=0.226 NS	r=0.067 NS

SSPS-R=Shalling-Sifneos Personality Scale-Revised, *MADRS*=Montgomery-Asberg Depression Rating Scale *TC*=Total Cholesterol, *H-DLC*=High-Density Lipoprotein Cholesterol, *L-DLC*=Low-Density Lipoprotein Cholesterol, *TR*=Ttriglycerides

studies comparing serum lipid profiles with AL in suicide attempters. This the first study to compare at the same time serum lipids, AL and depression in suicide attempters.

Several limitations of this preliminary study are worth noting: (a) Serum lipids were measured after attempted suicide and not before it; thus we were unable to control several conditions that may have affected serum lipid levels (b) Although subjects on drugs known to affect lipid levels were excluded, the absence of a washout period of psychotropic drugs should be taken into account (c) The relatively small sample of attempters by non-violent ways, limits the generalizability of our results in the whole group of suicide attempters.

The first finding of this study is the strong relationship detected between AL and depression in suicide attempters. This result is consisted with a previous study[20] and reinforces the hypothesis that subjects with AL are more prone to both depression and suicidality.[4] The second finding was that although there were no significant correlations between depression and serum lipids, there was an association between alexithymia and serum TR. Several mechanisms have been suggested to describe the potential effect of lipids metabolism on depression and/or suicidal behaviour. Perttinen[21] has suggested that lipid concentration and suicidal behaviour are possibly connected with interleukin-2, a cytokine produced by T cells that causes an increase in serum TR levels. Martin and Pihl[22] proposed the "stress-alexithymia" hypothesis in which patients with alexithymia may be suffering from chronic stress that, can promote increases in inflammatory factors such as interleukins and C-reactive protein.[23] According to Finset et al[24] alexithymia is related to high cortisol levels, which also, may increase the release of interleukins. Further studies are necessary to elucidate the relationship between alexithymia, depression and suicidality and the biological mechanisms involved in these conditions.

Αλεξιθυμία, κατάθλιψη και επίπεδα λιπιδίων ορού σε αποπειραθέντες αυτοκτονία

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Κατά τη διάρκεια της τελευταίας δεκαετίας αρκετές μελέτες έχουν διερευνήσει τη σχέση μεταξύ χοληστερόλης, κατάθλιψης και αυτοκτονίας. Ανάμεσα στις ειδικές ψυχολογικές παραμέτρους που σχετίζονται με το θυμικό είναι και η αλεξιθυμία. Η αλεξιθυμία έχει συσχετισθεί τόσο με την κατάθλιψη όσο και με την αυτοκτονική συμπεριφορά. Επίσης, αρκετές μελέτες υποστηρίζουν τη συσχέτιση ανάμεσα στα επίπεδα λιπιδίων ορού, την κατάθλιψη και την αυτοκτονική συμπεριφορά. Στη μελέτη αυτή εξετάσαμε την πιθανή συσχέτιση μεταξύ αλεξιθυμίας, κατάθλιψης και επιπέδου λιπιδίων σε αποπειραθέντες αυτοκτονία. Στη μελέτη συμπεριελήφθησαν 50 αποπειραθέντες αυτοκτονία με μη βίαιο τρόπο (υπέρβαση δοσολογίας φαρμάκων) με μέση ηλικία 35±12,2 ετών. Η αλεξιθυμία εκτιμήθηκε με τη χρήση της Αναθεωρημένης Κλίμακας Προσωπικότητας των Shalling-Sifneos (ΑΚΠΣΣ), και η κατάθλιψη, με την Κλίμακα Κατάθλιψης Montgomery-Asberg (ΚΚΜΑ). Τα επίπεδα λιπιδίων στον ορό προσδιορίστηκαν με ενζυματική μέθοδο μέσα σε 24 ώρες από την εισαγωγή των αποπειραθέντων αυτοκτονία στο νοσοκομείο. Η στατιστική ανάλυση έγινε με το στατιστικό πακέτο SPSS (έκδο-

ση 8,0), και χρησιμοποιήθηκε ο συντελεστής συσχέτισης του Spearman. Η μέση τιμή χοληστερόλης ορού (ΟΧ) των αποπειραθέντων ήταν 175,2 (±29,6) mg/dL, η μέση τιμή της υψηλής πυκνότητας χοληστερόλης (ΥΠΧ) ήταν 47,08 (±13,1) mg/dL, η μέση τιμή της χαμηλής πυκνότητας χοληστερόλης (ΧΠΧ) ήταν 109,5 (±23,5) mg/dL και η μέση τιμή των τριγλυκεριδίων ορού (ΤΡ) ήταν 89,4 (±39,1) mg/dL. Η μέση τιμή της ΑΚΠΣΣ ήταν (±3,7) και η μέση τιμή της ΚΚΜΑ ήταν 33,5 (±5,9). Βρέθηκαν σημαντικές συσχετίσεις ανάμεσα στην ΑΚΠΣΣ και την ΚΚΜΑ (r=0,439, p<0,001) όπως επίσης ανάμεσα στην ΑΚΠΣΣ και στα επίπεδα των ΤΡ (r=0,323, p<0,05). Δεν ανευρέθησαν σημαντικές συσχετίσεις ανάμεσα στην ΚΚΜΑ και στα επίπεδα των λιπιδίων ορού. Ελάχιστες μελέτες έχουν διερευνήσει τη συσχέτιση μεταξύ αλεξιθυμίας και άλλων κλινικών-ψυχοπαθολογικών παραμέτρων στους αποπειραθέντες αυτοκτονία. Δεν υπάρχουν προηγούμενες μελέτες που να διερευνούν τη σχέση ανάμεσα στα λιπίδια ορού και την αλεξιθυμία σε αποπειραθέντες αυτοκτονία. Η μελέτη αυτή είναι η πρώτη που διερευνά ταυτόχρονα τη σχέση ανάμεσα στα επίπεδα λιπιδίων ορού, την αλεξιθυμία και την κατάθλιψη σε αποπειραθέντες αυτοκτονία. Τα αποτελέσματα της μελέτης δείχνουν ότι αν και υπήρξε σημαντική συσχέτιση μεταξύ αλεξιθυμίας και κατάθλιψης στους αποπειραθέντες αυτοκτονία, μόνο η αλεξιθυμία συσχετίσθηκε με τα επίπεδα τριγλυκεριδίων ορού.

Λέξεις ευρετηρίου: Αλεξιθυμία, κατάθλιψη, λιπίδια ορού, απόπειρα αυτοκτονίας, υπέρβαση δοσολογίας φαρμάκων.

References

1. Sifneos PE. Alexithymia: past and present. *Am J Psyciatry* 1996, 153:137–142
2. Nemiah JC. Alexithymia; theoretical considerations. *Psychother Psychosom* 1977, 28:199–206
3. Sifneos PE. The prevalence of alexithymic characteristics in psychosomatic patients. *Psychother Psychosom* 1973, 22:255–262
4. Barenbaum H, Irvin S. Alexithymia, anger and interpersonal behavior. *Psychoter Psychosom* 1996, 65:203–208
5. Bankier B, Aigner M, Bach M. Alexithymia in DSM-IV disorder: comparative evaluation of somatoform disorder, panic disorder, obsessive-compulsive disorder, and depression. *Psychosomatics* 2001, 42:235–240
6. Saarijarvi S, Salminen JK, Toikka T. Temporal stability of alexithymia over a five-year period in outpatients with major depression. *Psychother Psychosom* 2006, 75:107–112
7. Arargum MY. Serum cholesterol concentration, depression and anxiety. *Acta Psychiatr Scand* 2002, 105:81-83
8. Lee HJ, Kim YK. Serum lipid levels and suicide attempts. *Acta Psychiatr Scand* 2003, 108:215–221
9. Vereza J, Zukov I, Morcinek T. Papezova H. Cholesterol concentrations in violent and non-violent women suicide attempters. *Eur Psychiatry* 2003, 18:23–27
10. Papacostas GI, Ongur D, Iosifescu DV, Mischoulon D, Fava M. Cholesterol in mood and anxiety disorders: review of the literature and new hypotheses. *Eur Neuropsychopharmacol* 2004, 14:135–142
11. De Berardis D, Conti CM, Serroni N, Moschetta FS, Carano A, Salerno RM et al. The role of cholesterol levels in mood disorders and suicide. *J Biol Regul Homeost Agents* 2009, 23:133–140
12. Sifneos PE. The Schaling-Sifneos Personality Scale-Revised. *Psychother Psychosom* 1986, 48:161–165
13. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979, 134:382–389
14. Muldoom MF, Manuck SB, Mathews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *BMJ* 1990, 301:309–314
15. Lindberg G, Rastam L, Gulberg B, Eklund GA. Low serum cholesterol concentration and sort-term mortality from injuries in men and women. *BMJ* 1992, 305:277–279
16. Tanskanen A, Vartiainen E, Tuomilehto J, Viinamaki H, Lehtonen J, Puska P. High serum cholesterol and risk of suicide. *Am J Psychiatry* 2000, 157:648–650
17. Borgherini G, Dorz S, Conforti D, Scarso C, Magni G. Serum cholesterol and psychological distress in hospitalized depressed patients. *Acta Psychiatr Scand* 2002, 105:149–152
18. Savark K, Acar B, Ak I. Alexithymia and suicidal behaviour. *Isr J Psychiatry Relat Sci* 2003, 40:165–173
19. Ianen I, Horesh N, Offer D, Dannon PN, Lepkifter E, Kotler M. Alexithymia, affect intensity and emotional range in suicidal patients. *Psychother Psychosom* 1999, 68:276–280
20. Taminen TJ, Saarijarvi S, Helenius H, Keskinen A, Korpilahti T. Alexithymia in suicide attempters. *Acta Psychiatr Scand* 1996, 93:195–198
21. Perttinen J. Hypothesis: low serum cholesterol, sucide and interleukin-2. *Am J Epidemiol* 1995, 141:716–718
22. Martin JB, Pihl RO. The stress-alexithymia hypothesis: theoretical and empirical considerations. *Psychother Psychosom* 1985, 43:169–176
23. De Berardis D, Serroni N, Campanella D, Carano A, Gambi F, Valchera A et al. Alexithymia an dits relationships with c-reactive protein and serum lipid levels among drug naive adult outpatients with major depression. *Progr Neuropsychopharmacol Biol Psychiatry* 2008, 32:1982–1986
24. Finset A, Graugaard PK, Holgersen K, Salivary cortisol response after a medical interview: the impact of physician communication behaviour, depressed affect and alexithymia. *Patient Educ Couns* 2006, 60:115–124

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General article
Γενικό άρθρο

The approach to melancholy on *30.1 Aristotelian problem*

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The *30.1 Aristotelian problem* is the most comprehensive and organized analysis of the phenomenon of melancholy in Aristotelian Corpus. Although, there are serious doubts if this text, as it was survived today, was written by Aristotle (384–322 B.C.) or by one of his followers –perhaps Theophrastus (372–287 B.C.)– nevertheless it is widely accepted that reflects the authentic ideas of Aristotle. The two counterbalancing sentiments, this of mirthfulness and this of moroseness, which are attributed in the text to the "melancholic" persons, introduce the primary difficulty, in order to be understood the unclear notion of melancholy in this work. All the previous approaches understood these sentiments, as diversity in the symptomatology of melancholy that is the ancient mental disorder which is similar to modern depression. But according to our point of view, this text is a study of pathological physiology, underling the significant role of black bile as the causative factor of the above two emotions in humans under the specific influence of temperature. Humor's overheat had as result the mirthfulness and its overcooling the moroseness. The reference to the healthy people and the graduation of the quantity of black bile in human body, as little, middle and massive, which is associated to the mentally ill persons, indicate that these two emotions were not only recognized as pathological manifestations of patients, but also as temperamental characteristics of healthy people, which arise from the same alteration of this humor, when its quantity is limited. Examining deeper the psychopathological aspect of this content, we may assume that, due to the fact mirthfulness was presented in the form of excessive enthusiasm, passion and courage and on the other hand moroseness by the distinctive elements of irrational fear, indolence and absurdity, the first one referred to mania and the second to melancholy, since their descriptions correspond to the basic features of each disease. Therefore, under the new reading, black bile should be perceived as the common source of the above two mental disorders, expressing the Aristotelian version of their correlation, which preoccupied many of the ancient Greek physicians as Themison (1st century B.C.) and his followers, Rufus of Ephesus (1st century A.D.), Galen (130–201 A.D.) and Aretaeus of Cappadocia (2nd century A.D.). This one probably derived from the difficulty to be fixed the limits

between these two diseases, because anger and fear could be present in both situations provoking the confusion. Finally, we should reject the hypothesis of bipolar disorder's presentation, because text's generality does not allow the limitation to only one pathological phenomenon, while the absence of particular data on the duration and sequence of the two different emotional states acts as a deterrent for such a conclusion.

Key words: *Aristotelian Problem 30. 1*, melancholy, bipolar disorders.

Introduction

The most extensive and well organized analysis of melancholy in Corpus Aristotelicum is found in the work, Problemata 30.1.[1] Although there are serious doubts if this text, as it is survived today, was written by Aristotle (384–322 B.C.) or by one of his followers –perhaps Theophrastus (372–287 B.C.)– nevertheless it is widely accepted that reflects the authentic ideas of Aristotle.[2]

The two counterbalancing sentiments, this of mirthfulness and this of moroseness, which are attributed in the text to the "melancholic" persons, introduce the primary difficulty, in order to be understood the unclear notion of melancholy in this work. In the previous interpretations, these two contravening sentiments were considered as two different manifestations of the patients suffering of melancholy.[3]

At this point, it should be pointed out that in antiquity the term "melancholy" was referring to the diseases which had as cause the excessive accumulation of black bile.[4] These included the mental disorder similar to modern depression and all the diseases of the body originated from this humor.

The term "melancholy" on *30.1 Aristotelian problem*

Aristotle used as pretext the introductory question, why distinguished intellectuals and politicians seem to be "melancholics", in order to present his theory about the role of black bile and its impact in human psychology. Under the influence of temperature started the disease of mania and melancholy, as they were perceived in antiquity.[1] Also this model was extended in healthy people, in order to explain their sentiments and comportments.

It is very important to remember that the term "melancholy" was never used in any work of Corpus Aristotelicum, nor in this one as one could expect, instead it was used the term "malancholics". The main subject here is black bile,[5] which is believed to be composed by heat or cold, whereas is cold by nature. The fundamental idea lies on its transformation. If becomes hooter, provokes cheerfulness and if colder, sullenness. This alteration is also reinforced by the other humor's element, the "pneuma", that is the air, which helps the changes of the temperature. Therefore, the comparison of black bile with wine and drunkenness was an evidential example of this theory due to their similarity in element components regarding the first one and its effect on the man regarding the second.[1]

Having in mind that the two counterbalancing sentiments are attributed in the text to "melancholics" and also that black bile is considered as "ēthopoios" (the factor which defines human moral),[1] we lead to the conclusion that the term "melancholics" should not be confused with the similar one used by ancient doctors for those who suffer from the mental disorder of melancholy. In this case, we believe that on *30.1 Aristotelian problem* are described the men, whose psychology is influenced by black bile, which under the above specific procedure will induce the two different results either in the form of the above two mental diseases, regarding ill people or as two counterbalancing temperaments, regarding the healthy.

The fact that mirthfulness was mainly presented in the text by over excitation and uncontrolled lust or gritt and on the other hand moroseness

by irrational fear, indolence and absurdity, which were the basic distinctive features in mania[6] and melancholy,[7] allows us to conclude that Aristotle by the term "melancholics" meant mania and melancholy (depression) too, having also in mind that he characterized these comportments as "manic" and "melancholic" manifestations.[2] According to the above, all the mythical or historic personages mentioned in the text, can be classified in each disease (Hercules, Ajax, Sibyllai, Bacchics, Marakos the Syracusian, Archelaos of Macedonia in mania and Bellerephon, Empedocles, Plato, Socrates in Melancholy).

Very useful was the example of suicide by hanging of young and elderly, which served as an explanatory lesson simultaneously for these two diseases and for the pathological mechanism of heat and cold, paralleled too to the analogous activity and effect of wine and drunkenness. That is the association of youth to heat and therefore mania and of old age to cold and melancholy.[1] Besides, it was widely accepted by the ancient Greek doctors that these two mental disorders were related to these groups.[8]

On the other hand, the resemblance of the above elements to the proportional feelings and the consecutive comportments presented in the personality of healthy people probably led to the acceptance that there is a common cause for both ill and healthy men, this of black bile.[1]

But this correlation entailed the risk of confusing healthy people with patients. Therefore it was necessary their distinction, which was achieved by the gradation of the quantity of black bile in the human body, as small, middle and massive. Limited amounts of the humor were linked to milder manifestations and associated to healthy people and on the other hand greater to acute symptoms and the patients.

This new interpretation convinces the discrepancy that can be raised in the birth or the understanding of these antithetical sentiments, if they are assigned only to melancholy. Besides, we should not forget that melancholy was distinguished from the other mental disorders by the moroseness which characterized the patients.[9]

The only question in this different approach concerns the absence of a definite declaration that overheated black bile can generate mania. But this idea, which in this text derives inferentially, was not out of the Aristotelian though, since it is declared in the Aristotelian work, *Problemata 1.12*.[1] About the introductory question, we assume that it was used as pretext, in order to be expounded the theory of the action of the black bile in human body, which was believed to have a fundamental role in the indissoluble relation of body and soul-mind.[10] In addition, this new reading comes in analogy with the problem of interrelation of mania and melancholy, which had preoccupied many ancient Greek doctors. This probably derived from the difficulty to be fixed the limits between these two disorders, because although the special clinical image of each disease indicated a different illness, the observation of anger and fear, which were probable in both situations and differentiated from the predominant characteristics in each case, even if they did not override them, provoked the confusion.

This one was expressed in many ways. The followers of Themison (1st century B.C.) had considered melancholy as a form of mania[11] as Caelius Aurelianus (5th century A.D.) informs us. Rufus of Ephesus (1st century A.D.)[12] and Galen (130–201 A.D.)[13] tried to describe a mechanism that produced black bile according to the principal that overheat of yellow bile, which was the main factor for mania, gave this result. Rufus of Ephesus added also overcooling, while pointing that melancholic humor can be present by nature to some people, letting us to believe that this Aristotelian Problem was his prototype, but replacing black bile with yellow.[12] Aretaeus of Cappadocia (2nd century A.D.) combined these two main ideas, thinking that melancholy is the start or part of mania presenting a pathological mechanism having as tool the dryness, which was an obvious result of overheat.[14] In conclusion, we should reject the hypothesis of bipolar disorder's presentation, because text's generality does not allow the limitation to only one disease, while the absence of particular data on the duration and sequence of the two different emotional states acts as a deterrent for such a conclusion.

Η προσέγγιση της μελαγχολίας στο *30.1 Πρόβλημα του Corpus Aristotelicum*

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Το *30.1 Πρόβλημα του Corpus Aristotelicum* (Αριστοτελικό Σύνταγμα) αποτελεί την πιο καλά δομημένη ανάλυση της μελαγχολίας που υπάρχει σε αυτή τη συλλογή. Παρά τις σοβαρές αμφιβολίες που γεννώνται για το αν το συγκεκριμένο κείμενο, όπως διασώθηκε, είναι γραμμένο από τον ίδιο τον Αριστοτέλη (384–322 π. Χ.) ή κάποιον από τους οπαδούς του –με πιο πιθανό τον Θεόφραστο (372–287 π. Χ.)– εντούτοις θεωρείται ότι εκφράζει τις πραγματικές αριστοτελικές αντιλήψεις. Τα δύο αντίρροπα συναισθήματα, της ευθυμίας και της δυσθυμίας, που αποδίδονται στους «μελαγχολικούς», συνιστούν την κύρια δυσκολία στο να γίνει αντιληπτή η ασαφής έννοια της μελαγχολίας σε αυτό το έργο. Σε όλες τις προηγούμενες προσεγγίσεις τα παραπάνω έγιναν αντιληπτά ως πολυμορφία στη συμπτωματολογία της μελαγχολίας, δηλαδή της ψυχικής νόσου στην αρχαιότητα που προσομοίαζε στη σύγχρονη κατάθλιψη. Κατά την άποψή μας, το κείμενο αυτό στην πραγματικότητα αποτελεί μια μελέτη παθολογικής φυσιολογίας, στην οποία παρουσιάζεται η αριστοτελική ιδέα για τον καταλυτικό ρόλο της μέλαινας χολής ως αιτιολογικού παράγοντα διαμόρφωσης των δύο συγκεκριμένων συναισθημάτων στον άνθρωπο. Ο μηχανισμός γέννησής τους στηρίχθηκε στη μεταβολή της θερμοκρασίας του χυμού, ώστε η υπερθέρμανσή του να προκαλεί την ευθυμία και η ψύξη του τη δυσθυμία. Όμως, η αναφορά στους υγιείς και η διαβάθμιση της ποσότητας της μέλαινας χολής στο ανθρώπινο σώμα σε μικρή, μεσαία και μεγάλη, με την τελευταία να αναγνωρίζεται στους ψυχικά πάσχοντες, υποδεικνύει ότι τα δύο συναισθήματα δεν περιορίζονταν μόνο ως παθολογικές εκδηλώσεις των ασθενών, αλλά λειτουργούσαν ακόμη και ως γνωρίσματα της ιδιοσυγκρασίας των υγιών, τα οποία προέκυπταν από το ίδιο σχήμα. Όσον αφορά στο ψυχοπαθολογικό περιεχόμενο, επειδή η ευθυμία δηλώθηκε με τη μορφή του υπέρμετρου ενθουσιασμού, πάθους και θάρρους και η δυσθυμία με τα διακριτικά στοιχεία του παράλογου φόβου, της νωχέλειας και της μωρίας, μας επιτρέπεται να υποθέσουμε ότι η πρώτη παρέπεμπε στη νόσο της μανίας και η δεύτερη σε εκείνη της μελαγχολίας, αφού αυτές οι περιγραφές αντιστοιχούσαν στα βασικά χαρακτηριστικά των δύο ασθενειών, όπως τα αντιλαμβάνονταν στην αρχαιότητα. Σύμφωνα με τη νέα ερμηνεία, η μέλαινα χολή γίνονταν αντιληπτή ως η κοινή πηγή των δύο νόσων, ώστε με αυτό τον τρόπο να εκφράζεται η αριστοτελική εκδοχή του συσχετισμού τους, που απασχόλησε αρκετούς από τους αρχαίους έλληνες ιατρούς, όπως τον Θεμίσωνα (1ος π.Χ. αιώνας) και τους οπαδούς του, τον Ρούφο τον Εφέσιο (1ος μ.Χ. αιώνας), τον Γαληνό (130–201 μ.Χ.) και τον Αρεταίο τον Καππαδόκη (2ος μ.Χ.). Αυτός ο συσχετισμός πιθανότατα ήταν το αποτέλεσμα της δυσκολίας στον καθορισμό των ορίων των δύο ψυχικών διαταραχών, επειδή η οργή και ο φόβος που αποτελούσαν ειδικά γνωρίσματα της μανίας και της μελαγχολίας αντίστοιχα, ήταν δυνατό να εμφανιστούν και στις δύο αυτές καταστάσεις, προκαλώντας σύγχυση. Τέλος, θα πρέπει να απορρίψουμε την υπόθεση της διπολικής διαταραχής, γιατί η γενικότητα των αναφορών φανερώνει ότι δεν αφορά αποκλειστικά σε ένα μόνο παθολογικό φαινόμενο, ενώ η απουσία σαφών στοιχείων ως προς τη χρονική έκταση και τη διαδοχή των δύο διαφορετικών συναισθηματικών καταστάσεων λειτουργούν ανασταλτικά ως προς αυτή την ταύτιση.

Λέξεις ευρετηρίου: *Αριστοτελικό πρόβλημα 30.1*, μελαγχολία, διπολική διαταραχή.

References

1. Aristoteles. Problemata In: Bekker I (ed) *Aristotelis opera*. Academia Regia Borussica, Berlin, 1831
2. van der Eijk PJ. *Medicine and Philosophy in Classical Antiquity. Doctors and Philosophers on Nature, Soul, Health and Disease*. Cambridge University Press, Cambridge, 2005:166–167
3. Simon B. *Mind and Madness in Ancient Greece: The Classical Roots of Modern Psychiatry*. Cornell University Press, Ithaca NY, 1978:230
4. Galenus Med. De atra bile. In: Boer W de (ed) *Galeni de atra bile libellus, Corpus medicorum Graecorum*. Teubner, Leipzig, 1937
5. Kudlien F. *Der Beginn des medizinischnen Denkens bei den Griechen von Homer bis Hippokrates*. Zurich, 1967:77–99
6. Pigeaud J. Prolégomènes à une histoire de la mélancolie*. Histoire, Economie, Société* 1984, 3:501–510
7. Leven KH (ed) *Antike Medizin.* Ein Lexicon. Beck CH, München, 2005:601–603
8. Pigeaud J. *La maladie de l' âme*. Etude sur la relation de l' âme et du corps dans la tradition médico-philosophique antique. Thèse de doctorat, Paris, 1981
9. Flashar H. *Melancholie und Melancholiker in den medizinischen Theorien der Antike*. de Gruyter, Berlin, 1966
10. Chaignet AE. *Histoire de la psychologie des Grecs*. Hachette, Paris, 1893
11. Drabkin IE. *Caelius Aurelianus on Acute and Chronic Diseases*. The University of Chicago Press, Chicago, 1950
12. Αλtius Med. Iatricorum liber vi. In: Olivieri A (ed) *Aëtii Amideni libri medicinales v-viii*. Corpus medicorum Graecorum. Berlin, 1950
13. Galenus Med. Hippocratis prorrheticum i commentaria iii. In: Diels H (ed) *Galeni in Hippocratis prorrheticum i commentaria iii*. Corpus medicorum Graecorum. Leipzig, 1915
14. Aretaeus Med. De causis et signis acutorum morborum. In: Hude K (ed) *Aretaeus, Corpus medicorum Graecorum*. Berlin, 1958

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Case report
Ενδιαφέρουσα περίπτωση

Glandular cystitis and lithium intoxication in a patient with bipolar disorder

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A 42-year-old woman, with a 12-year history of bipolar disorder was referred to our department due to tremor, sedation, dysarthria, polyuria and polydipsia. She had been on lithium monotherapy during the last 3 years. On admission, her cognitive status was intact, and neither depression nor euphoria was reported. Lithium plasma levels were 1.6 mEq/L, whereas creatinine and urea levels were 2.8 IU/L and 110 IU/L, respectively. The patient did not take other medications or misused lithium. Lithium was immediately discontinued. Ultrasound scans of the urinary tract were suggestive of bilateral hydronephrosis secondary to bladder contraction and cystoscopy-guided bladder biopsy revealed glandular cystitis a benign tumour into the bladder's wall, which impeded the bladder's contraction leading to hydronephrosis and subsequent toxic lithium plasma levels. The patient was switched to valproate and was referred for surgical excision of the lesion. One year later, she was in good physical and mental health under treatment with valproate (1000 mg/day). This is the first case report of grandular cystitis leading to lithium intoxication by impairing renal function. Acute renal failure leading to lithium intoxication would be possible. However, a thorough imaging, endoscopical and histological study revealed glandular cystitis as the cause of renal impairment. Although physicians are alert about lithium's toxicity and a monitoring of renal function is routinely prescribed, little focus has been made on the integrity of the urinary tract. We suggest that urinary tract imaging should be part of the routine work-up in patients presenting with symptoms and signs of lithium intoxication, since concomitant urinary tract lesions might occasionally be the cause of renal impairment leading to reduced lithium excretion.

Key words: Glandular cystitis, lithium, intoxication, bipolar disorder.

Introduction

Lithium has been a gold standard in the treatment of bipolar disorder and its efficacy has been documented in numerous trials.[1] However, its use is complicated by low therapeutic index. Dosing must be guided by monitoring of serum levels, so that the risk of severe toxicity is reduced. Potential causes of lithium intoxication include drug overdose, dehydration, a low-sodium diet, interactions with concomitant medications, and renal impairment. In cases of lithium intoxication, immediate discontinuation of the regimen and supporting of renal function is indicated.[2]

We present the case of a female bipolar patient who manifested lithium intoxication which was finally attributed to renal impairment caused by a benign urinary bladder lesion.

Case report

A 42-year-old woman, with a 12-year history of bipolar I disorder was referred to our Department, because she gradually manifested over a period of one week tremor, sedation, dysarthria, polyuria and polydipsia. She had been stabilized on a lithium 660 mg/day regimen during the last 3 years. Lithium plasma levels were routinely monitored and the last plasma level recorded –2 months before the admission– was 0.8 mEq/L. Five years ago, the patient was diagnosed with endometrial cancer which had been successfully treated.

On admission, she was well oriented in time, place and person, and reported no feelings of sadness or euphoria. Lithium plasma levels were found toxic (1.6 mEq/L), whereas creatinine and urea levels were 2.8 IU/L and 110 IU/L, respectively. The rest of serum chemistry assays as well as thyroid function tests were unremarkable. The patient denied taking other medications apart from lithium or ingesting higher doses of lithium. Dehydration (e.g. due to infection, excessive sweating or diarrhoea) was excluded on the basis of serum chemistry and history. Lithium was immediately discontinued. Ultrasound scans of the urinary tract were suggestive of bilateral hydronephrosis. Cystoscopy-guided bladder biopsy finally revealed glandular cystitis, a benign urinary bladder lesion.[3] The patient was switched to valproate and was referred to an urologist for specialist management. One year later, she was in good physical and mental health under treatment with valproate 1000 mg/day (plasma levels 60 μg/mL).

Discussion

The most common renal side effect induced by chronic lithium administration is a defect in urine concentrating ability; patients on long-term therapeutic doses of lithium often complain of polyuria, nocturia and thirst while about 10% may manifest nephrogenic diabetes insipidus.[4] Lithium rarely causes serious but most often reversible glomerular filtration rate reductions and renal failure due to interstitial nephritis acutely or progressively over the years, especially after episodes of lithium intoxication.[5,6] Furthermore, there are occasional reports of usually reversible, lithium-related nephrotic syndrome and incomplete distal renal tubular acidosis.[4,5] In such cases, clinicians usually discontinue lithium, support renal function and switch to another mood stabilizing agent.

Renal impairment was the most probable cause of lithium intoxication in our patient; our first thought was that acute renal failure was induced by chronic lithium treatment per se.[4,5] Our decision to request further evaluation was driven by the patient's history of endometrial cancer and the possibility of secondary metastases. A thorough imaging, endoscopical and histological study finally revealed a benign urinary bladder lesion which had led to hydronephrosis, renal impairment and subsequent toxic lithium plasma levels. Physicians are alert about lithium's toxicity and a monitoring of renal function is routinely prescribed. However, when renal impairment is the suspected cause of lithium intoxication, clinicians usually withdraw lithium while usually omitting an imaging study of the urinary tract. Little focus is made on the integrity of the urinary tract, although obstructions can also impair lithium renal excretion. Moreover, in clinical practice psychiatric patients do not undergo frequent laboratory check-ups although they often suffer from underdiagnosed somatic comorbidities.[7]

Cystitis glandularis is a metaplastic alteration of the urothelium in the urinary bladder that is thought to be induced by chronic inflammation or irritation.[3]

This is the first case report recording an association between chronic lithium administration and cystitis glandularis. This may be a chance finding, given that lithium is not generally considered to be carcinogenic in humans.[8] However, lithium has been reported to promote bladder carcinogenesis in rats.[9]

In conclusion, we suggest that when renal impairment is the suspected cause of lithium intoxication urinary tract imaging should be part of patients' workup, since concomitant urinary tract lesions might occasionally be the cause of renal impairment leading to reduced lithium excretion.

Αδενική-διάμεση κυστίτιδα και τοξίκωση από λίθιο σε ασθενή με διπολική διαταραχή

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Γυναίκα 42 ετών με ιστορικό διπολικής διαταραχής από 12 ετίας παραπέμφθηκε στο τμήμα μας, λόγω τρόμου, καταστολής, δυσαρθρίας, πολυουρίας και πολυδιψίας. Βρισκόταν σε μονοθεραπεία με λίθιο κατά τη διάρκεια των 3 τελευταίων ετών. Κατά την εισαγωγή της, οι γνωστικές λειτουργίες ήταν ακέραιες, ενώ δεν ήταν παρούσα σημειολογία κατάθλιψης ή ευφορίας. Τα επίπεδα λιθίου στο πλάσμα ήταν 1,6 mEq/L, και οι τιμές κρεατινίνης και ουρίας 2,8 IU/L και 110 IU/L, αντίστοιχα. Η ασθενής δεν ελάμβανε άλλα φάρμακα ούτε υψηλότερη δόση του λιθίου από τη συνταγογραφούμενη. Η χορήγηση λιθίου διακόπηκε αμέσως. Το υπερηχογράφημα του ουροποιητικού συστήματος ανέδειξε δευτεροπαθή υδρονέφρωση και η καθοδηγούμενη από κυστεοσκόπηση βιοψία της ουροδόχου κύστεως ανέδειξε αδενική-διάμεση κυστίτιδα, καλοήθη νεοπλασματική εξεργασία, στο τοίχωμα της ουροδόχου κύστεως, η οποία οδήγησε σε υδρονέφρωση και στη συνέχεια σε τοξικά επίπεδα του λιθίου στο πλάσμα. Η ασθενής ετέθη σε αγωγή με βαλπροϊκό οξύ και παραπέμφθηκε για χειρουργική εκτομή της βλάβης. Ένα χρόνο αργότερα, η ασθενής ήταν σε καλή σωματική υγεία και σταθεροποιημένη υπό θεραπεία με βαλπροϊκό (1000 mg/ημ). Πρόκειται για την πρώτη περίπτωση που περιγράφεται στη βιβλιογραφία, όπου αδενική-διάμεση κυστίτιδα οδηγεί σε τοξικά επίπεδα λιθίου και νεφρική δυσλειτουργία. Αν και η οξεία νεφρική ανεπάρκεια ως συνεπακόλουθη της δηλητηρίασης από λίθιο θα ήταν δυνατή, μια λεπτομερής απεικονιστική, ενδοσκοπική και ιστολογική μελέτη ανέδειξε ότι η αδενική-διάμεση κυστίτιδα ήταν η αιτία της νεφρικής ανεπάρκειας. Η διενέργεια συμπληρωματικού απεικονιστικού ελέγχου του ουροποιητικού συστήματος σε ασθενείς με συμπτώματα δηλητηρίασης από λίθιο συνιστάται, δεδομένου ότι βλάβες του ουροποιητικού συστήματος μπορεί περιστασιακά να οδηγήσουν σε νεφρική δυσλειτουργία και στη συνέχεια σε μειωμένη απέκκριση λιθίου.

Λέξεις ευρετηρίου: Αδενική-διάμεση κυστίτιδα, λίθιο, τοξίκωση, διπολική διαταραχή.

References

1. Fountoulakis KN, Vieta E. Treatment of bipolar disorder: a systematic review of available data and clinical perspectives. *Int J Neuropsychopharmacol* 2008, 11:999–1029
2. Freeman MP, Freeman SA. Lithium: clinical considerations in internal medicine. *Am J Med* 2006;119:478-481
3. Sung MT, Lopez-Beltran A, Eble JN, MacLennan GT, Tan PH, Montironi R et al. Divergent pathway of intestinal metaplasia and cystitis glandularis of the urinary bladder. *Mod Pathol* 2006, 19:1395–1401
4. Boton R, Gaviria M, Batlle DC. Prevalence, pathogenesis and treatment of renal dysfunction associated with chronic lithium therapy. *Am J Kidney Dis* 1987, 10:329–345
5. Gitlin M. Lithium and the kidney: an updated review. *Drug Saf* 1999, 20:231–243
6. Fenves AZ, Emmett M, White MG. Lithium intoxication associated with acute renal failure. *South Med J* 1984, 77:1472–1474
7. Maier W, Falkai P. The epidemiology of comorbidity between depression, anxiety disorders and somatic diseases. *Int Clin Psychopharmacol* 1999, 14(Suppl 2):S1–6
8. Leonard A, Hantson P, Gerber GB. Mutagenicity, carcinogenicity and teratogenicity of lithium compounds. *Mutat Res* 1995, 339: 131–137
9. Frolov AG, Pliss GB. The lithium carbonate promotion of urothelial tumors in rats induced with N-butyl-N-(4-hydroxybutyl)-nitrosamine. *Vopr Onkol* 1992, 38:1309–1313

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Case report
Ενδιαφέρουσα περίπτωση

A case of pregabalin intoxication

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Pregabalin, or S-(+)-3-isobutylgaba, is a lipophilic analogue of GABA. Although pregabalin is structurally related to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically. Pregabalin is a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system. It is currently being licensed for epilepsy, neuropathic pain, and generalized anxiety disorder. There are few case reports that have demonstrated safety of pregabalin in case of intoxication. We report here a case of pregabalin toxicity with a moderate pregabalin concentration that was successfully managed with conservative treatment only. The case report describes a 54-year-old man who was treated with pregabalin for generalized anxiety disorder. After having experienced a significant stress on a job the patient ingested huge amount of pregabalin (4,2 r) together with bromazepam (21 mg) and chlorimipramine (125 mg). On presentation he was conscious and alert with a stable condition of cardiovascular and respiratory systems. The serum pregabalin concentration was 20.8 mg/L but the patient did not have any signs of toxicity. Thanks to his good and stable somatic condition the patient was managed with supportive treatment only. Although anecdotal, our case report points toward safety of pregabalin following deliberate self-poisoning. Our observation is in accordance with the recent international literature underlining that pregabalin was listed as the drug injested in only 1% of fatalities, usually in combination with other drugs.

Key words: Pregabalin, intoxication, psychopharmacology, anxiety.

Introduction

Pregabalin, or S-(+)-3-isobutylgaba, is a lipophilic analogue of GABA substituted at the 3-position to facilitate diffusion across the blood-brain barrier. Although pregabalin is structurally related to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically.[1,2] Pregabalin is a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system. The alpha-2-delta site is an auxiliary protein associated with voltage-gated calcium channels. The binding of pregabalin and its structural analogues at the alpha-2-delta site has been shown

to reduce depolarization-induced calcium influx at nerve terminals, with a consequential reduction in the release of several excitatory neurotransmitters, including glutamate, noradrenalin, substance P, and calcitonin gene-related peptide (CGRP).[3–5] Pregabalin has no effects on GABA-ergic mechanisms. It is currently being licensed for epilepsy, neuropathic pain, and generalized anxiety disorder.[6,7]

We report here a case of isolated pregabalin toxicity with the highest recorded pregabalin concentrations to date that was successfully managed with conservative treatment only.

Case report

A 54-year-old male, with no relevant medical history, has been treated with 450 mg of pregabalin daily for generalized anxiety disorder. After having experienced a significant stress on a job the patient ingested 4.2 g of pregabalin together with 21 mg of bromazepam and 125 mg of chlorimipramine in order to relax. On presentation he was conscious and alert with a Glasgow Coma Score (GCS) of 30, cardiovascularly stable with a heart rate of 84 bpm and blood pressure of 110/70 mmHg, with a temperature of 36.8 °C and respiratory rate of 18/min. Pregabalin concentrations were measured in the plasma sample that had been obtained on admission using a previously described method.[2] Pregabalin concentration at the time of admission was 20.8 mg/L. A comprehensive toxicological screening of urine by gas chromatography mass-spectrometry detected only chlorimipramine and bromazepam which he had also ingested. As he was clinically stable on presentation, he had neither an electrocardiogram (ECG) nor arterial blood gases or renal function performed. The patient was admitted more then two hours after ingestion and as he was clinically stable he was not administered any drug and was observed for signs of clinical deterioration for one day. The clinical toxicology review was undertaken and it was decided that the patient should be managed with general supportive care only, anticipating spontaneous recovery. He remained cardiovascularly stable, with no signs of deterioration of his consciousness. As the patient had no ongoing features of pregabalin toxicity he was discharged after one day and his psychiatric treatment continued.

Discussion

We have described here a case of severe toxicity following self-poisoning, with pregabalin, bromazepam and chorimipramine. The serum pregabalin concentration in this patient of 20.8 mg/L is moderate compared to those previously reported, but we managed the patient with supportive treatment only.

Very little information is available regarding therapeutic serum/plasma concentrations of pregabalin. However, one report states that in samples collected at random times relative to dose from patients maintained on 600 mg/day, plasma pregabalin concentrations ranged from 0.9–14.2 mg/L.[8]

There are three previous reported cases of pregabalin toxicity following deliberate self-poisoning.[9–11] One patient presented with mild drowsiness following ingestion of an unknown amount of pregabalin and required supportive management only; that patient had pregabalin concentration of 29 mg/L 9 h post-ingestion.[10] The other case was a patient who ingested 11.5 g of pregabalin, together with 32 g of lamotrigine, who initially developed abnormal facial and generalised body movements and drowsiness.[9] The "initial" pregabalin plasma concentration was approximately 60 mg/L, but the sample also contained lamotrigine at a concentration of approximately 45 mg/L. Finally, the third patient had "initial" pregabalin plasma concentration of about 65 mg/L and had developed coma after 3 hours.[11]

Apart from these case reports, there is limited information available about the frequency of pregabalin self-poisoning. For example, the American Association of Poison Control Centers annual reports do not include data on pregabalin, except when it was involved in a fatality.[12] In terms of pregabalin-associated fatalities in these annual reports, pregabalin was not mentioned in any fatalities prior to 2006. Between 2006 and 2008, pregabalin was listed as a drug used/ingested in approximately 1% of fatalities; none of these cases were isolated pregabalin cases.[12]

Pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations within an hour of dosing and up to 90% oral bioavailability.[9] Pregabalin undergoes negligible metabolism in humans (<2% metabolism) and is excreted virtually unchanged by the kidneys. Pregabalin does not bind to plasma proteins.[13] It is also not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the cytochrome P450 system. Unwanted clinical effects, including dizziness, somnolence, weight gain, psychosis and myoclonus, have been reported during therapeutic use of pregabalin at doses of 50–600 mg/day.[14,15]

Pregabalin has a low volume of distribution (approximately 0.5 L/kg), low molecular weight (approximately 159 Da) and is not protein bound.[16] These pharmacokinetic features make it likely that elimination of pregabalin would be enhanced by the use of extra-corporeal methods such as haemodialysis and/or haemofiltration. Our case report describes a patient with a moderate serum pregabalin concentration who was managed with supportive treatment only and did not have any signs of toxicity. Although anecdotal, our case report points toward safety of pregabalin following deliberate self-poisoning.

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Περίπτωση τοξίκωσης από πρεγκαμπαλίνη

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Η πρεγκαμπαλίνη ή S(+)-ισοβουτυλο-γ-αμινοβουτυρικό οξύ είναι λιπόφιλο ανάλογο του GABA (γ-αμινοβουτυρικού οξέος). Αν και η πρεγκαμπαλίνη σχετίζεται δομικά με το GABA είναι ανενεργή στους υποδοχείς του GABA και δεν φαίνεται να μιμείται τη φυσιολογία του GABA. Η πρεγκαμπαλίνη δεσμεύεται ισχυρά στην άλφα-2-δέλτα (α2δ) υπομονάδα των τασεοεξαρτώμενων διαύλων ασβεστίου στο Κεντρικό Νευρικό Σύστημα. Έχει λάβει άδεια χρήσης στην επιληψία, στον νευροπαθητικό πόνο και στη διαταραχή γενικευμένου άγχους. Υπάρχουν ελάχιστες αναφορές περιπτώσεων που καταδεικνύουν την ασφάλεια της πρεγκαμπαλίνης σε περιπτώσεις υπερδοσολογίας. Παρουσιάζεται περίπτωση τοξικότητας πρεγκαμπαλίνης με μέτρια συγκέντρωση πρεγκαμπαλίνης στον ορό σε σύγκριση με τις προαναφερθείσες περιπτώσεις και που αντιμετωπίστηκε επιτυχώς μόνο με συντηρητική αγωγή. Η περίπτωση αφορά σε 54χρονο που ελάμβανε πρεγκαμπαλίνη για διαταραχή γενικευμένου άγχους. Μετά την εμφάνιση ιδιαίτερα έντονου στρες στην εργασία του, ο ασθενής έλαβε μεγάλη ποσότητα πρεγκαμπαλίνης (4,3 g) σε συνδυασμό με βρωμαζεπάμη (21 mL) και χλωριμιπραμίνη (125 mg). Η συγκέντρωση πρεγκαμπαλίνης στον ορό ήταν 20,8 mg/L αλλά ο ασθενής δεν είχε σημεία τοξικότητας. Χάρη στη σταθερά καλή σωματική του κατάσταση, ο ασθενής αντιμετωπίσθηκε με υποστηρικτική αγωγή μόνο. Η περίπτωση αυτή, αν και μεμονωμένη, παρέχει ενδείξεις υπέρ της ασφάλειας της πρεγκαμπαλίνης μετά από λήψη υπερβολικής δόσης. Η παρατήρησή μας έρχεται σε συμφωνία με την πρόσφατη διεθνή βιβλιογραφία όπου επισημαίνεται το γεγονός ότι η πρεγκαμπαλίνη έχει εκτιμηθεί ότι συμβάλλει μόνο κατά 1% στη θνησιμότητα από δηλητηριάσεις, συνήθως συγχορηγούμενη με άλλα φάρμακα.

Λέξεις ευρετηρίου: Πρεγκαμπαλίνη, τοξίκωση, ψυχοφαρμακολογία, άγχος.

References

1. Yoo L, Matalon D, Hoffman RS, Goldfarb DS. Treatment of pregabalin toxicity by haemodialysis in a patient with kidney failure. *Am J Kidney Dis* 2009, 54:1127–1130
2. Berry D, Millington C. Analysis of pregabalin at therapeutic concentrations in human plasma/serum by reversed phase HPLC. *Ther Drug Monit* 2005, 27:451–456
3. Fink K, Dooley DJ, Meder WP et al. Inhibition of neuronal Ca(2^+) influx by gabapentin and pregabalin in the human neocortex. *Neuropharmacology* 2002, 42:229–236
4. Dooley DJ, Donovan CM, Pugsley TA. Stimulus-dependent modulation of [3H]norepinephrine release from rat neocortical slices by gabapentin and pregabalin. *J Pharmacol Exp Ther* 2000, 295:1086–1093
5. Dooley DJ, Mieske CA, Borosky SA. Inhibition of K(+)-evoked glutamate release from rat neocortical and hippocampal slices by gabapentin. *Neurosci Lett* 2000, 280:107–110
6. Ben-Menachem E, Kugler AR. Pregabalin and epilepsy. In: Shorvon S, Fish D, Dodson W, Perruca (eds) *Treatment of Epilepsy*. 2nd edition. Oxford, Blackwell Publishing Ltd, Oxford (in press)
7. Ben-Menachem E, Kugler AR. Pregabalin. In: Levy RH, Mattson RH, Meldrum BS, Perucca E (eds) *Antiepileptic drugs*. 5th edition. Philadelphia: Lippincott Williams & Wilkins, 2002:901–905
8. French JA, Kugler AR, Garafalo EA, Robbins JL, Anhut H, Messmer S. Pregabalin dose-response in patients with partial seizures as evaluated in two add-on trials. *Epilepsia* 2001, 42(Suppl 2):36
9. Braga AJ, Chidley K. Self-poisoning with lamotrigine and pregabalin. *Anaesthesia* 2007, 62:524–527
10. Spiller HA, Bratcher R, Griffiths JRK. Pregabalin overdose with benign outcome. *Clin Tox* 2008, 46:917
11. Wood DM, Berry DJ, Glover G, Eastwood J, Dargan PI. Significant pregabalin toxicity managed with supportive care alone. *J Med Toxicol* 2010, 6:435–437
12. American Association of Poison Control Centers. Annual data reports. http://www.aapcc.org/dnn/NPDSPoisonData/AnnualReports/tabid/125/Default.aspx. Last accessed 1 Feb 2010
13. Kugler AR, Robbins JL, Strand JC, svi autori et al. *Pregabalin overview: a novel CNS-active compound with anticonvulsant activity*. Poster presented at the Annual Meeting of the American Epilepsy Society, Seattle, Washington, 6–11, 2002
14. Olaizola I, Ellger T, Young P, Boseback F, Evers S, Kellinghaus C. Pregabalin-associated acute psychosis and epileptiform EEG-changes. *Seizure* 2006, 15:208–221
15. Huppertz HJ, Feuerstein TJ, Schulze-Bonhage A. Myoclonus in epilepsy patients with anticonvulsive add-on therapy with pregabalin. *Epilepsia* 2001, 42:790–792
16. Pfizer Limited. Lyrica capsules – summary of product characteristics. Pfizer Limited, UK. http://emc.medicines.org.uk/document. aspx?documentId=14651. Last accessed 1 Feb 2010

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Books review
Βιβλιοκριτική

C.S. Ierodiakonou
The psychology of Aristotle:
A psychoanalytic therapist's perspective
Karnac, London, 2011:166

There are some aspects that are unique in Aristotle. The diversity of subjects he excelled in, from poetry to astronomy and from mathematics to ethics, and the reference to him as "the" philosopher, are clear recognition and appreciation of his immense contribution.

Professor Charalampos Ierodiakonou, a distinguished Professor of (significantly) the "Aristotelian" University of Thessaloniki, deals with the psychology of Aristotle. He is one of the most apt persons to do so, being a psychoanalytically oriented psychiatrist, a gifted scholar, a charismatic teacher, and the author of several well-received books on Aristotle.

The book is divided into five parts: Part I deals with the soul-body problem about which Aristotle accepts a psychosomatic unity (like today's psychobiological model).

In Part II the mental functions are described in detail. The ancient philosopher distinguishes sense-perception, thought, judgement, volition, psychomotor function, affect, memory and consciousness as the main psychic processes. One is astonished at Aristotle's ability to observe not only what is evident on the surface, but to explain intrapsychic phenomena with theories and ideas which are very close to the object of modern dynamic psychology, e.g. repression.

In Part III the views of Aristotle concerning the formation of personality are examined. The philosopher accepts different constitutional potentialities for each individual, but the significant influence of the parental environment and teachers in the shaping of a child's personality is clearly expressed.

Part IV concerns the interpersonal relations, since Aristotle in many of his books considers Man as a social and political being (zoon politikon). Mother's relationship with her children is considered by the philosopher the ideal love, the one that offers everything "in joys and in sorrows". Friendship also is approached by Aristotle from many angles. He underlines the psychosocial necessity of friendship for everyone. Aristotle connects erotic love with the passion and drives of youth and describes many emotional manifestations of love affairs. His approach is what we would today call bio-psycho-social.

The last Part V deals with observations and theories of the philosopher which are very close to psychoanalytic ideas or concepts, e.g. repression, hedone, latent dreams etc.

I feel confident that this new book will bring Aristotle's teaching closer to us and will enhance our understanding of the ideas of the philosopher on a diachronic aspect of life – the human psyche.

George N. Christodoulou,
Emeritus Professor of Psychiatry
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Χ.Σ. Ιεροδιακόνου
Η ψυχολογία κατά τον Αριστοτέλη:
Η άποψη του ψυχαναλυτή - θεραπευτή»
Καρνάκ, Λονδίνο, 2011

Ο Χαράλαμπος Ιεροδιακόνου, Καθηγητής Ψυχιατρικής του Αριστοτέλειου Πανεπιστημίου Θεσσαλονίκης, χαρισματικός δάσκαλος, ψυχαναλυτής, συγγραφέας πολλών βιβλίων σχετικά με τα κείμενα του Αριστοτέλη, θεωρείται ο πλέον κατάλληλος προκειμένου να γράψει για την «Ψυχολογία κατά τον Αριστοτέλη». Το βιβλίο χωρίζεται σε πέντε ενότητες. Η πρώτη ενότητα καλύπτει θέματα που αφορούν στη σχέση ψυχής-σώματος υιοθετώντας την ψυχοσωματική διάσταση (ψυχοβιολογικό μοντέλο). Η δεύτερη ενότητα περιγράφει τις ψυχιατρικές λειτουργίες και δίνει εξηγήσεις σε ενδοψυχικά φαινόμενα. Η τρίτη ενότητα ασχολείται με τη διαμόρφωση της προσωπικότητας, με ιδιαίτερη έμφαση στο οικογενειακό περιβάλλον και την εκπαίδευση. Η τέταρτη ενότητα καλύπτει τις διαπροσωπικές σχέσεις επισημαίνοντας την κοινωνική και πολιτική συνείδηση του ατόμου. Η πέμπτη ενότητα αναφέρεται σε θεωρητικές απόψεις και παρατηρήσεις του Αριστοτέλη που βρίσκονται πολύ κοντά στις σύγχρονες ψυχαναλυτικές σκέψεις. Το βιβλίο αυτό, πιστεύουμε, θα φέρει κοντά μας την Αριστοτελική σκέψη και διδασκαλία και θα μας βοηθήσει να κατανοήσουμε τις φιλοσοφικές του ιδέες σε μια διαχρονική διάσταση του ανθρώπινου ψυχισμού.

Γεώργιος Ν. Χριστοδούλου,
Ομότιμος Καθηγητής Ψυχιατρικής

Βασίλης Π. Κονταξάκης,
Καθηγητής Κλινικής και Κοινωνικής Ψυχιατρικής

Future scientific meetings
Προσεχείς επιστημονικές εκδηλώσεις

- **Διεθνές Συνέδριο της Παγκόσμιας Ομοσπονδίας Ψυχικής Υγιεινής (WFMH)**
  3ο Μονοθεματικό Συνέδριο της Ελληνικής Ψυχιατρικής Εταιρείας (ΕΨΕ)
  «Κρίση και καταστροφές: Ψυχοκοινωνικές επιπτώσεις»,
  Ξενοδοχείο Royal Olympic, Αθήνα
  6–9 Μαρτίου 2013
  Οργάνωση: Ελληνική Ψυχιατρική Εταιρεία, World Federation for Mental Health, Εταιρεία Προληπτικής Ψυχιατρικής
  Πληροφορίες: Επιστημονική Γραμματεία: ΕΨΕ, Παπαδιαμαντοπούλου 11, 115 28, Αθήνα,
  Τηλ: (+30) 210-72 14 184,
  Fax: (+30) 210-72 32 042, E-mail: psych@psych.gr, Website: www.psych.gr
  Οργανωτική Γραμματεία: ERA LTD, Ασκληπιού 15, 106 80, Αθήνα,
  Τηλ: (+30) 210-36 34 944, Fax: (+30) 210-36 31 690,
  E-mail: info@era.gr, Website: www.era.gr

- **International Society of Affective Disorders, 2012 Congress, London UK**
  18–20 April 2012
  Organizer: ISAD
  Conference Secretariat: Kenes UK, London, UK
  Tel: +44(0) 2073838030, Fax: +44(0) 2073838040
  E-mail: (a) isad@kenes.com
  (b) isad@isad.org.uk

- **"XIV National Congress of the Serbian Psychiatric Association, "Psychiatry for a Changing World", Belgrade, Serbia**
  18–21 April 2012
  Contacts: Prof Slavica Djukic-Dejanovic,
  Prof Dusica Lecic-Tosevski
  Organizer: Serbian Psychiatric Association
  Collaboration: Psychiatric Association of Eastern Europe and the Balcans (PAEEB)
  E-mail: spacongress2012@gmail.com
  Website: www.ups-spa.org

- **"8th International Conference on Psychiatry", "Co-morbidity within Psychiatric disorders and Medical Illnesses"Jeddah, Kingdom of Saudi Arabia**
  17–19 April 2012
  Organizer: (a) Saudi German Hospital (SGH)
  (b) Saudi Psychiatric Association
  Collaboration: (a) Okasha Institute of Psychiatry, Ain Shams University
  (b) Egyptian Psychiatric Association
  Contact: Dr. Mohamed Khaled
  E-mail: moh.khaled.hamed@gmail.com

- **XXVII Argentine Congress of PsychiatryQ"Professional Responsibilities in the face of Social Suffering and Mental Disorders", Buenos Aires, Argentina**
  18–21 April, 2012
  Organisers: Argentinean Psychiatrists Association (APSA)
  Collaboration: Association of Psychiatry of Rosario
  Contact: Dr. Graciela Onofrio and Dr. Alfredo H. Cía
  E-mail: secretaria@apsa.org.ar
  Web: www.apsa.org.ar

- **Addictive disorders, Beirut, Lebanon**
  20–21 April, 2012
  Organizer: Lebanese Society of Psychiatry
  Collaboration: Saint Joseph University.
  Contact: Prof. Charles Baddoura
  E-mail: Charlesb@dm.net.lb

- **"First Maghrebian Conference on Psychiatry Residency Education", Sousse Tunisia**
  25–28 April, 2012
  Organizer: Maghrebian Society of Psychiatry

Collaboration: (a) World Federation of Societies of Biological Psychiatry,
(b) Arab Federation of Psychiatrists
Contact: Prof. Bechir BEN HADJ ALI
E-mail: bechir_benhadjali@yahoo.fr
Website: www.smpsy.com

- **Doha Undergraduate Psychiatry Workshop, Doha, Qatar**
27–28 April, 2012
Organizer: Weill Cornell Medical College in Qatar
Collaboration: Asian Federation of Psychiatric Associations
Contact: Dr. Ziad Kronfol
E-mail: zik2002@qatar-med.cornell.edu

- **2nd Certified Training Course: Training in the use of psychometric and neuropsychological tests, Thessaloniki, Greece**
19 May 2012
Organizer: International Society on Neurobiology and Psychopharmacology (ISNP)
Collaboration: WPA Section on Private Practice
Contact: Dr. Kostas N. Fountoulakis
E-mail: kfount@med.auth.gr
Website: www.psychiatry.gr

- **"Annual Meeting of the Royal Australian and New Zealand College of Psychiatrists" with the theme "Cells, Circuits and Syndromes", Tasmania, Australia**
20–24 May 2012
Organizer: The Royal Australian and New Zealand College of Psychiatrists
Contact: Helen McGowan
E-mail: helen@wsm.com.au
Website: www.ranzcp2012.com

- **Σύγκρουση και συμφιλίωση: Στις ομάδες, στα ζεύγη, στις οικογένειες, στην κοινωνία», Αθήνα**
24–27 Μαΐου 2012
Οργάνωση: (α) Ευρωπαϊκή Ομοσπονδία Ψυχαναλυτικής Ψυχοθεραπείας (ΕΟΨΨ)
(β) Ελληνική Εταιρεία Ομαδικής Ανάλυσης & Οικογενειακής Θεραπείας
Οργ. Γραφείο: Easy Travel, Τηλ: (+30) 210-36 15 201, Fax: (+30) 210-36 25 572
E-mail: secretariat@efppathens2012.gr

- **1sr Instanbul-Eurasian Regional Congress of Biological Psychiatry, Instanbul, Turkey**
27–31 May 2012
Contact: Prof Bilgen Taneli
Organizer: Turkish Society of Biological Psychiatry
Website: www.biologicalpsychiatry-instanbul2012.org

- **"International Symposium on Controversies in Psychiatry", "Predictive indicators of response to Psychopharmacologic medications", Cancún, México**
30 May–1 June, 2012
Organizer: APAL
Contact: Prof. Enrique Camarena
Email: camarena@avantel.net/camarena@ControversiasMexico.org
Website: www.ControversiasMexico.org/www.apalweb.org

- **4ο Πανελλήνιο Ψυχιατρικό Συνέδριο στην Πρωτοβάθμια Φροντίδα Υγείας, Κυλλήνη Ηλείας**
1–4 Ιουνίου 2012
Οργάνωση: Ψυχιατρική Κλινική Πανεπιστημίου Πατρών
Επικοινωνία: Αναπλ. Καθ. Φ. Γουρζής
Τηλ: (+30) 2610-990 559, Fax: (+30) 2610-994 534
E-mail: pgourzis@upatras.gr

- **8ο Διεθνές Ψυχαναλυτικό Συμπόσιο Δελφών, Δελφοί, Ελλάς**
1–4 Ιουνίου 2012
Θέμα: «Ο πατέρας»
Οργ. Γραφείο: Easy Travel
Αναγνωστοπούλου 19, 10673 Αθήνα
Τηλ: (+30) 210-36 15 201, 210-36 09 442,
Fax: (+30) 210-36 25 572
E-mail: easytravel@hol.gr
Επιστ. Γραμματεία: Ε. Βουγά
Ψυχιατρική Κλινική Πανεπιστημίου Πατρών, 265 04 Ρίο, Πάτρα
Τηλ: (+30) 2610-992 996, Fax: (+30) 2610-994 534
E-mail: evouga@upatras.gr

- **5th International Together Against Stigma Conference, Ottawa, Canada**
4–6 June, 2012
Organizers: Mental Health Commission of Canada
Collaboration: WPA Scientific Section on Stigma and Mental Disorders
Contact: Dr. Heather Stuart/Ms. Jayda Wiebe
E-mail: jwiebe@mentalhealthcommission.ca
Website: www.togetheragainststigma2012.ca

- **30th Nordic Congress of Psychiatry, Tromso, Norway**
5–8 June 2012
Organizer: (a) Norwegian Psychiatric Association
(b) Joint Committee of the Nordic Psychiatric Associations
Contact: Dr. Tore Sørlie
E-mail: Tore.Sorlie@unn.no
Website: www.ncp2012.org

- **"XXV Congress of the Spanish Association of Neuropsychiatry", Tenerife, Spain**
  6–9 June 2012
  Organizers: (a) Spanish Association of Neuropsychiatry
  (b) Canary Association of Neuropsychiatry
  Contact: Dr. Francisco Rodríguez Pulido
  E-mail: fpulido@ull.es/tibanez@ultramarevents.com
  Website: http://congresoaen12.com

- **1ο Πανελλήνιο Συνέδριο Κλινικής Ψυχοφαρμακολογίας, Costa Navarino Hotel, Πύλος Μεσσηνίας**
  21–24 Ιουνίου 2012
  Οργ. Φορέας: Ελληνική Ψυχοφαρμακολογική Εταιρεία
  Οργ. Γραφείο: ONE TO ONE A.E., Ναυάρχου Νικοδήμου 2, 105 57 Αθήνα
  Επικοινωνία: Αν. Καθ. Β. Αλεβίζος
  Τηλ: (+30) 210-72 54 383-95-6, Fax: (+30) 210-72 54 384
  E-mail: info@onetoone-congress
  Website: www.psychology/onetoone-congress.gr

- **"WPA Regional Meeting", Tehran, Iran**
  31 May–2 June 2012
  Contact: Dr Ahmed Jalili
  Organizer: Iranian Psychiatric Association
  E-mails: info@psychiatrist.ir, sajalili@gmail.com
  Website: www.psychiatrist.ir

- **"Strategies for Responding to Psychiatric Challenges" Moscow, Russia**
  28 June–1 July 2012
  Organizers: (a) Russian Society of Psychiatrists (RSP)
  (b) International Society of Quality Medicine (ISoQM)
  Organizing Secretariat: Global Events Ltd
  50A Stadiou street, GR-555 35 Pylea, Thessaloniki, Greece
  Tel: (+30) 2310313-631, Fax: (+30) 2310-247 746
  Website: www.globalevents.gr

- **15th International Philosophy and Psychiatry Conference, Dunedin, New Zealand**
  5–7 July 2012
  Organizers: Philosophy, Psychiatry and Psychology Interest Group-University of Otago
  Collaboration: (a) International Network for Philosophy and Psychiatry (INPP)
  (b) WPA Section of Philosophy and Humanities
  Contact: Prof. Grant Gillett/Dr. Adriano C. T. Rodrigues
  E-mail: grant.gillett@stonebow.otago.ac.nz/actrodrigues@gmail.com
  Website: http://www.events4you.co.nz/inpp2012.html

- **"Clinical Challenges in Psychosomatic Medicine", Moscow, Russia**
  5–7 July 2012
  Organizer: (a) International Society of Quality Medicine
  (b) Russian Society of Psychiatrists
  Contact: Dr A. Vidalis
  E-mail: athvidalis@gmail.com
  Website: http://www.is-qm.eu/is-qm.eu/Moscow,_RUSSIA.html

- **25η Πανελλήνια Εκπαιδευτική Συνάντηση Ειδικευομένων Ψυχιάτρων, θέμα: «Αυτοκτονικότητα», Λουτράκι**
  6–8 Ιουλίου 2012
  Οργάνωση: (α) Ελληνική Ψυχιατρική Εταιρεία (ΕΨΕ)
  (β) Ένωση Ελλήνων Ειδικευομένων Ψυχιάτρων (ΕΕΕΨ)
  Οργανωτική Γραμματεία: Ελένη Γκρέτσα, ΕΨΕ
  Επικοινωνία: Καθ. Β. Κονταξάκης, Α. Οικονόμου
  Τηλ: (+30) 210-77 58 410, 210-72 14 184, 6942-950 257, 6974-715 296, Fax: (+30) 210-77 58 405, 210-72 42 032
  E-mail: editor@psych.gr

- **"International Congress of the Royal College of Psychiatrists 2012", "Psychiatry: medicine and the future", Liverpool, UK**
  10–13 July 2012
  Organizers: Royal College of Psychiatrists
  Contact: Dr. Helen Miller
  E-mail: congress@rcpsych.ac.uk
  Website: http://www.rcpsych.ac.uk/events/international-congress2012.aspx

- **12th Berlin Summer School: Psychiatry as a Science, Learning and Plastisity, Berlin, Germany**
  26–31 August 2012
  Organizer: Department of Psychiatry and Psychotherapy, Clarité Campus Mitte, Clarité-Universitätsmedizin Berlin
  Contact: Prof Andreas Ströhle
  Tel: (+49) 30450517034
  E-mail: andreasstroehle@charite.de

- **"International Conference on Bioethics Education", Tiberias, Israel**
  2–5 September 2012
  Organizer (a) UNESCO,
  (b) The International Centre for Health, Law and Ethics, University of Haifa
  Collaboration: (a) WPA Section on Disaster Intervention (b) WPA Section on psychiatry in developing countries
  Contact: Yaffa Collins
  E-mail: artemisa@netvision.net.il
  Website: www.isas.co.il/bioethics2012

- **WPA Regional Meeting"Mental Health and Disaster: Beyond Emergency Response", Bali, Indonesia**
  13–15 September, 2012
  Organizer: Indonesian Psychiatric Association
  Collaboration:Asian Federation for Psychiatry & Mental Health (AFPMH)
  Contact: Dr. Tun Kurniasih Bastaman
  E-mail: tunbastaman@yahoo.com

- **26η Πανελλήνια Εκπαιδευτική Συνάντηση Ειδικευομένων Ψυχιάτρων, 2nd International Psychiatric Trainees Conference, θέμα: "Psychiatric Education and Training in Europe", Πόρτο Χέλι**
  14–16 Σεπτεμβρίου 2012
  Οργάνωση: (α) Ελληνική Ψυχιατρική Εταιρεία (ΕΨΕ) (β) Ένωση Ελλήνων Ειδικευομένων Ψυχιάτρων (ΕΕΕΨ)
  Οργ. Γραμματεία: Ε. Γκρέτσα, ΕΨΕ
  Επικοινωνία: Καθ. Β. Κονταξάκης, Α. Οικονόμου, Χρ. Τσόπελας
  Τηλ: (+30) 210-77 58 410,210-72 14 184, 6942-950 257, 6974-715 296, 6945-733 371 Fax: (+30) 210-77 58 405
  E-mail: editor@psych.gr, psych@psych.gr

- **Second international congress of suicidal behaviour, Pasto - Colombia**
  20–22 September, 2012
  Organizer: Health sciences program – University of Nariño
  Collaboration: Latin American psychiatric association (APAL)
  Contact: Prof. Castulo Cisneros Rivera
  E-mail: cfcisr@gmail.com
  Website: www.udenar.edu.co

- **11th European Federation of Sexology Congress, "Promoting Sexual Health: "a pathway to happiness", Madrid, Spain**
  20–22 September, 2012
  Organizers: European Federation of Sexology
  Contact: Dr. Chiara Simonelli/Dr. Miren Larrazabal
  E-mail: efs2012@aimgroup.eu
  Website: web.aimgroupinternational.com/2012/efs

- **5th International Conference of Schizophrenia (ICONS), Chennai, India**
  21–23 September, 2012
  Organizers: Schizophrenia Research Foundation
  Contact: Dr. R. Thara
  E-mail: thara@scarfindia.org
  Website: www.icons-scarf.org

- **"Fourth International Congress of Psychiatry", "Integrated Psychiatry" , Ain-Sokhna, Egypt**
  27–28 September 2012
  Organizers: Psychiatry Department, Al Azhar University
  Collaboration: Egyptian Psychiatric Association
  Contact: Prof. Hashem Bahary
  E-mail: omik121@hotmail.com

- **Annual meeting of the Societe de l'Information Psychiatrique, Lyon, France**
  3–6 October, 2012
  Organizer: Societe de l'Information Psychiatrique
  Contact: Marc Betremieux
  E-mail: secretariataefcp@gmail.com

- **"1st International Psychiatric Conference in Palestine", "Community Mental Health and Recent Advance in Psychotropic Drugs", Ramallah, Palestine**
  11–12 October, 2012
  Organizers: Palestinian Psychiatric Association
  Contact: Dr. Ziad Arandi
  E-mail: dr_arandi@hotmail.com
  Website: www.ppsya.ps

- **Third Congress of Psychiatry in Bosnia and Herzegovina, "Psychiatry between Phenomenology and Neuroscience", Tuzla, Bosnia and Herzegovina**
  12–15 October, 2012
  Organizers: Psychiatric Association of Bosnia-Herzegovina
  Collaboration: University Clinical Center Tuzla, Psychiatry Department
  Contact: Professor Izet Pajević/Dr. Mevludin Hasanović
  E-mail: hameaz@bih.net.ba
  Website: http://www.upubih.com/3kongres

- **25th ECNP Congress, Vienna, Austria**
  13–17 October 2012
  Organizer: European College of Neuropharmacology (ECNP)
  Contact: ECNP Office
  Tel: (+31) 302538567
  Website: www.ecnp.eu

- **"WPA International Congress", Prague, Czech Republic**
  17–21 October 2012
  Contact: Dr Jiri Raboch
  Organizer: Czech Psychiatric Association
  E-mail: wpaic2012@guarant.cz
  Website: www.wpaic2012.org

- **"Suicide Prevention for Young People", Budapest, Hungary**
  19–21 October, 2012
  Organizers: Lelekben otthon foundation
  Collaboration: (a) Hungarian Psychiatric Association
  (b) British Choose Life program

Contact: Karoly Oriold, Aron Szasz
E-mail: info@lelekbenotthon.hu
Website: www.lelekbenotthon.hu

- **"XX Annual Conference of the Bulgarian Psychiatric Association", "Psychiatry-medical standard and practices", Borovetz, Bulgaria**
  2–4 November 2012
  Organizer: Bulgarian Psychiatric Association
  Collaboration: (a) Balkan association for philosophy, psychiatry and psychology
  (b) International network for philosophy of psychiatry
  Contact: Prof. D. Stoyanov
  Email: drozdstoj@uni-plovdiv.bg
  Website: http://www.bpabg.com/?q=en/home, http://www.cic.bg/index_eng.html

- **"1st International Conference on Cultural Psychiatry in Mediterranean Countries", "Acculturative stress and coping with cultural transition", Tel-Aviv, Israel**
  5–7 November 2012
  Organizers: WPA Section on Transcultural Psychiatry
  Collaboration: Israeli Psychiatric Association
  Contact: Dr. Anne-Marie Ulman
  E-mail: am.ulman8@gmail.com
  Website: www.wpa-tps.tel-aviv2012.com

- **"Body and Art – the Image of Hysteria in the 21st Century", Vienna, Austria**
  14–16 November, 2012
  Organizer: WPA Section on Art and Psychiatry
  Collaboration: (a) Vienna Art Week
  (b) Institut français,
  (c) Sigmund Freud Privatstiftung
  (d) Groupe de Recherches Pandora et CRPMS (Centre de Recherches Psychanalyse, Médecine et Société, Université Paris-Diderot)
  (e) World Psychiatric Association Section on Art and Psychiatry
  Contact: Dr. Hans-Otto Thomashoff
  E-mail: dr@thomashoff.de

- **XXVII APAL Congresswith the theme: "Identity and validity of Latin American Psychiatry: Unity in Diversity", Buenos Aires, Argentina**
  16–19 November, 2012
  Organizers: APAL (Latin American Psychiatry Association)
  Collaboration: APSA (Argentinean Psychiatrists Association)
  Contact: Dr. Alfredo Cia and Dr. Enrique Camarena Robles
  E-mail: secretaria@apalcongreso2012.org
  Website: www.apalcongreso2012.org

- **19th Annual Conference of Indian Association for Social Psychiatry "Migration and Mental Health", Chandigarh, India**
  23–25 November 2012
  Organizers: Indian Association for Social Psychiatry
  Collaboration: World Association for Social Psychiatry (WASP)
  Contact: Prof. B.S. Chavan
  E-mail: drchavanbs@yahoo.com, psygmch@hotmail.com
  Website: www.iasp.org.com

- **The first Interdisciplinary Congrerss: Psychiatry and Related Sciences, Divani Caravel Hotel, Athens, Greece**
  29 November–2 December 2012
  Organizers: World Psychiatric Association, International Neuropsychiatric Association, Hellenic Society for the Advancement of Psychiatry and Related Sciences
  Organizing Bureau: Erasmus Conferences Tours & Travels SA, Kolofontos & Evridikis street 161 21 Athens, Greece
  Contact: Prof P. Soldatos
  Tel: (+30) 210-74 14 700, Fax: (+30) 210-72 57 532
  E-mail: info@psych-relatedsciences.org
  Website: www.psych-relatedsciences.org

- **Διεθνές Συνέδριο της Παγκόσμιας Ομοσπονδίας Ψυχικής Υγιεινής (WFMH)**
  3ο Μονοθεματικό Συνέδριο της Ελληνικής Ψυχιατρικής Εταιρείας
  «Κρίση και καταστροφές: Ψυχοκοινωνικές επιπτώσεις»,
  Ξενοδοχείο Royal Olympic, Αθήνα
  6–9 Μαρτίου 2013
  Οργάνωση: Ελληνική Ψυχιατρική Εταιρεία, World Federation for Mental Health, Εταιρεία Προληπτικής Ψυχιατρικής
  Πληροφορίες: Επιστημονική Γραμματεία: ΕΨΕ, Παπαδιαμαντοπούλου 11, 115 28 Αθήνα
  Τηλ: (+30) 210-72 14 184, Fax: (+30) 210-72 32 042
  E-mail: psych@psych.gr, Website: www.psych.gr
  Οργανωτική Γραμματεία: ERA LTD, Ασκληπιού 15, 106 80 Αθήνα, Τηλ: (+30) 210-36 34 944, Fax: (+30) 210-36 31 690
  E-mail: info@era.gr, Website: www.era.gr

- **11th Workshop on Costs and Assessment in Psychiatry - Mental Health Policy, Economics and Health Care Reforms, Venice, Italy**
  22–24 March, 2013
  Organizer: WPA Section on Mental Health Economics
  Contact: Dr. Massimo Moscarelli
  E-mail: moscarelli@icmpe.org
  Website: www.icmpe.org

- **WPA Regional Congress, Bucharest, Romania**
  10–13 April, 2013
  Organizer: Romanian Psychiatric Association
  Contact: (a) Dr. Dan Prelipceanu

(b) Dr. Eliot Sorel
E-mail: (a) Dr. Dan Prelipceanu, prelipceanudan@yahoo.com
(b) Dr. Eliot Sorel, esorel@gmail.com
Website: www.wpa2013bucharest.org

- **WPA Regional Congress "Facilitating Mental Health, Primary Care and Public Health Integration", Bucharest, Romania**
10–13 April 2013
Contact: Prof Eliot Sorel
Tel: (+40) 212105814, Fax: (+40) 212122702
E-mail: secretariat@wpa2013bucharest.org
Website: www.wpa2013bucharest.org

- **3rd Congress of Neurobiology, Psychopharmacology and Treatment Guidance, Thessaloniki, Greece**
30 May–2 June 2013
Organizer: International Society of Neurobiology & Psychopharmacology
Contact: Ast. Prof. K. N. Fountoulakis
Organizing Secretariat: Global Events Ltd
Tel: (+30) 2310-313 631, Fax: (+30) 2310-247 746
Website: www.globalevents.gr

- **"WPA Third Thematic Conference on Legal and Forensic Psychiatry, Madrid, Spain**
12–14 June 2013
Organizer: Spanish Society of Legal Psychiatry
Contact: Dr Alfredo Calcedo Barba
E-mail: alfredocalcedo@gmail.com

- **"WPA International Congress", Istanbul, Turkey**
19–23 June 2013.
Organizer: (a) Psychiatric Association of Turkey
(b) Turkish Neuropsychiatric Society
Contact: Dr. Levent Kuey
E-mail: kueyl@superonline.com

- **21st World Congress of Social Psychiatry "The bio-psycho-social Model: the Future of Psychiatry", Lisbon, Portugal**
29 June–3 July 2013
Organizer: World Association for Social Psychiatry
Contact: Professor Driss Moussaoui
E-mail: drissm49@gmail.com
Website: www.wasp2013.com

- **"4th European Conference on Schizophrenia Research (ECSR)", "Together for better treatment and care", Berlin, Germany**
26–28 September, 2013
Organizers : (a) European Scientific Association on Schizophrenia and other Psychoses
(b) Competence Network on Schizophrenia (CNS)
(c) European Psychiatric Association and its Section on Schizophrenia
(d) German Association for Psychiatry and Psychotherapy (DGPPN)
Collaboration: WPA section on Schizophrenia
Contact : Viktoria Toeller
E-mail: toeller.viktoria@uni-duesseldorf.de
Website: www.schizophrenianet.eu

- **"WPA Thematic Conference", "Human Factors in Crisis and Disasters - Future proofing of crisis and disaster management", Melbourne, Australia**
30 September– 3 October, 2013.
Organizer: Indo Australasian Psychiatry Association
Collaboration: (a) WPA Section on Disaster Psychiatry
(b) UNESCO Chair in Bioethics
Contact: Dr. Russell D'Souza
E-mail; russell.f.dsouza@gmail.com
Website: www.wpadisasterpsych.com

- **"26th ECNP Congress, Barcelona, Spain**
5–9 October 2013
Organizer: European College of Neuropharmacology (ECNP)
Contact: ECNP Office
Tel: (+31) 302538567
E-mail: nice2012@ecupeu
Website: www.ecnp.eu

- **2nd Congress on Treatment in Psychiatry, Ostrava, Czech Republic**
10–13 October, 2013
Organizer: Czech Psychiatric Association
Contact: Prof. Jiri Raboch, M.D.
Email: lecbavpsychiatrii2013@guarant.cz
Website: www.lecbavpsychiatrii2013.cz

- **"WPA International Congress", "Future Psychiatry: Challenges and Opportunities", Vienna, Austria**
27–30 October, 2013.
Organizer: Austrian Association for Psychiatry and Psychotherapy
Contact: Prof. Michael Musalek
E-mail: wpaic2013@guarant.cz
Website: www.wpaic2013.org

- **"WPA Regional Meeting", "Addressing mental health needs in the Alps-Adria-Danube Region: Stigma, Community Based Care, Stress and Suicidality", Ljubljana, Slovenia**
9–12 April, 2014
Organizer: Psychiatric Association of Slovenia
Contact: Dr. Peter Pregelj/Dr. Jurij Bon

E-mail: peter.pregelj@psih-klinika.si/
jurij.bon@pb-begunje.si

Website: www.wpaljubljana2014.org

- **Congress of World Association for Dynamic Psychiatry "Multidisciplinary Approach to and Treatment of Mental Disorders: Myth or Reality?", St. Petersburg, Russia**

14–17 May, 2014

Organizer: World Association for Dynamic Psychiatry

Contact: Dr. Maria Ammon, General Secretary WADP

E-mail: DAPBerlin@aol.com

Website: www.wadp-congress.de

- **"WPA 16th World Congress of Psychiatry", "Focusing on Quality, Access and Humane Care", Madrid, Spain**

14–18 September, 2014

Organizer: Spanish Society of Psychiatry (SEP)

Collaboration: (a) Spanish Association of Neuropsychiatry (AEN)

(b) Portuguese Society of Psychiatry and Mental Health (SPPSM)

Contact: Ms. Carolina G. Sicilia

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