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Editorial
Άρθρο σύνταξης

Psychotropic medication in pregnancy: The cost-benefit ratio revised

Psychiatriki 2015, 26:165–168

The use of drugs during pregnancy and breast-feeding is a long-lasting debate among scientists. Many of them support the view that the risks are minimal, since the anomalies in fetuses due to chemical compounds are approximately 1%,[1] while others argue that the effects of drug delivery in this special period of life has largely unknown delayed consequences.[2] In clinical practice the dilemma is to prescribe or not to prescribe a drug during pregnancy.

Recent scientific data indicate direct adverse effects due to the state of the mental health of the mother to the fetus and, possibly, an increased risk of developing serious mental disorders in children whose mothers did not receive medication during pregnancy.[3] Given the uncertainty of the data, the optimal way of managing the problem is to educate the clinicians regarding available research data, to develop an individualized risk-benefit analysis, and finally to inform the mother and, where feasible, the father.

Currently, the choice is based on a five category classification A, B, C, D and X. Regulatory authorities such as the EMA, FDA, etc. have established the five categories to indicate the potential of a drug to cause birth defects if used during pregnancy. The categories are determined by the reliability of documentation and the risk to benefit ratio. They do not take into account any risks from pharmaceutical agents or their metabolites in breast milk. An extra category N has been adopted where there are no data available.

In reality this classification has certain limitations. For example we have two antipsychotic drugs. The first drug is classified as B and the second one as C. How certain is that the first is safest than the second one? The answer is we don't really know. A drug with studies in animals and reports in humans can be classified in category C, while another drug just because it has limited studies or use, which did not show relevant problems, can be classified in category B and then after data accumulation can be re-classified as C or D.

In general, summarized data for all the categories of the psychotropics do not show significant teratogenic effects. There are cautions for tricyclic antidepressants, some anticonvulsant and lithium (until completion of the organogenesis of the heart).[4,5] The administration of psychotropic drugs during breast-feeding is clearly more restrictive, due to the potential toxicity in the newborn and the infant, and the existence of the safer alternative of the human-like milk. Furthermore, a drug is rarely falls within the exclusion category (x) without figures to support this restriction.

In practice a lot of information is collected from the traditional pregnancy registries, i.e. prospect observational studies, which monitor pregnant women from the time of entry in the registry until a short time after birth and detect major teratogenic incidents. These registries have significant limitations, such as small samples, inability to control the population, and limited follow-up. The presence of confounders such as tobacco use, alcohol consumption, and folic acid prescription during pregnancy can complicate the interpretation of the results.

The traditional classification of the five categories is simplistic and often confuses over the complexity and ambiguity of the final choice. The limitations have led to the development of alternative methods for the assessment of the risk of medication use in pregnant women. The broader cooperation of regulatory authorities worldwide is fundamental. Since December 2014, FDA published the New Pregnancy and Lactation Labelling Rule (PLLR),[6] which has already been implemented for all new drugs by June 30, 2015, and gradually retroactively for drugs that have been licensed from 2001 and beyond. The new classification is based, like the previous one, in the traditional pregnancy registries, but also in the design of larger cohort studies, databases

of civil claims of persons who have suffered damage, and the wider cooperation of the parties involved (regulatory agencies, scientists, users etc.). Finally this new PLLR forms a new parameter, which relates to the effect of drugs on the females and males reproductive potential.

The landscape in the use of drugs in pregnancy is significantly altered after the accumulation of research. Data show that the risks from the use of drugs in pregnancy and lactation are probably overestimated, while the various diseases and conditions may have multiple adverse effects both on mothers and children.[3,7] The administration of any psychotropic drug during pregnancy is based on an integrated risk assessment plan. Parents are required to have an active role in the final decision, helped by a clear and comprehensive cost-benefit analysis from their physicians.

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Άρθρο σύνταξης
Editorial

Φάρμακα και κύηση: Αναθεωρώντας το ισοζύγιο οφέλους-κόστους

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Η χρήση φαρμάκων κατά την κύηση και τον θηλασμό έχει αποτελέσει από μακρού θέμα αντιπαράθεσης μεταξύ των επιστημόνων. Πολλοί υποστηρίζουν την άποψη ότι οι κίνδυνοι είναι ελάχιστοι, αφού μόλις το 1% των ανωμαλιών στα έμβρυα οφείλονται σε χημικούς παράγοντες,[1] ενώ αντίθετα άλλοι υποστηρίζουν ότι οι επιπτώσεις της χορήγησης φαρμάκων σε αυτή την ιδιαίτερη περίοδο της ζωής έχει, εν πολλοίς, άγνωστες μακροχρόνιες συνέπειες.[2] Στην κλινική πράξη το δίλημμα είναι να συνταγογραφήσει ή να μη συνταγογραφήσει κάποιος φάρμακα κατά την κύηση.

Τα πρόσφατα ερευνητικά στοιχεία δείχνουν άμεσες δυσμενείς επιπτώσεις της κατάστασης της ψυχικής υγείας της μητέρας στο έμβρυο, και ενδεχομένως αυξημένη πιθανότητα ανάπτυξης μειζόνων διαταραχών σε παιδιά των οποίων οι μητέρες δεν έλαβαν φαρμακευτική αγωγή κατά την κύηση.[3] Με δεδομένη την αβεβαιότητα των στοιχείων, η ασφαλέστερη μέθοδος διαχείρισης του προβλήματος είναι η εκπαίδευση των κλινικών ως προς τα ερευνητικά δεδομένα, η ανάπτυξη εξατομικευμένης ανάλυσης κινδύνου-οφέλους, και τέλος η ενημέρωση της μητέρας αλλά και –όπου αυτό είναι εφικτό– του πατέρα.

Η επιλογή μέχρι σήμερα βασίζεται στις πέντε κατηγορίες A,B,C,D και X χαρακτηρισμού της επικινδυνότητας χρήσης ενός φαρμάκου κατά την κύηση, οι οποίες έχουν θεσπισθεί από τις διάφορες ρυθμιστικές αρχές, όπως η EMA, FDA κ.ά. και αναφέρονται στα δεδομένα ασφαλείας κάθε φαρμακευτικού προϊόντος για ανθρώπινη χρήση. Οι κατηγορίες αυτές αντανακλούν θεωρητικά τη σχετική επικινδυνότητα ενός φαρμάκου με αύξουσα σειρά. Μια ακόμη κατηγορία N έχει υιοθετηθεί όταν δεν υπάρχουν διαθέσιμα δεδομένα. Η πραγματικότητα όμως είναι ότι η κατηγοριοποίηση αυτή έχει εξαιρετικά σημαντικούς περιορισμούς. Για παράδειγμα αν έχουμε ένα αντιψυχωτικό φάρμακο κατηγορίας B και ένα κατηγορίας C, πόσο βέβαιο είναι ότι το πρώτο είναι ασφαλέστερο του δεύτερου; Η απάντηση είναι ότι δεν γνωρίζουμε. Το πρώτο φάρμακο για το οποίο έχουν γίνει μελέτες σε πειραματόζωα και υπάρχουν αναφορές από ανθρώπους, έχει ταξινομηθεί στην κατηγορία C, ενώ το δεύτερο, επειδή απλώς έχει περιορισμένες μελέτες οι οποίες δεν έδειξαν προβλήματα, στην κατηγορία B, και στη συνέχεια μετά από σώρευση στοιχείων είναι δυνατόν να ταξινομηθεί ως C ή D.

Από τις κατηγορίες των ψυχιατρικών φαρμάκων περιληπτικά τα στοιχεία δείχνουν ότι δεν εμφανίζουν ουσιώδη κίνδυνο τερατογένεσης. Επιφυλάξεις υπάρχουν για τα τρικυκλικά αντικαταθλιπτικά, κάποια αντιεπιληπτικά και το λίθιο (μέχρι την ολοκλήρωση της οργανογένεσης της καρδιάς).[4,5] Η χορήγηση ψυχοτρόπων φαρμάκων κατά τον θηλασμό είναι σαφώς πιο περιοριστική, αφενός λόγω πιθανότητας τοξικότητας στο νεογνό και το βρέφος, αφετέρου λόγω της δυνατότητας χορήγησης ασφαλούς εξανθρωποποιημένου γάλακτος. Από την άλλη πλευρά, δεν είναι σπάνιο το φαινόμενο ένα φάρμακο να εντάσσεται στην κατηγορία αποκλεισμού (X) χωρίς τα στοιχεία να υποστηρίζουν αυτόν τον αποκλεισμό. Στην πράξη πολλές πληροφορίες συλλέγονται από τα μητρώα κυήσεων, δηλαδή από προοπτικές μελέτες παρατήρησης, οι οποίες παρακολουθούν τις εγκύους από τον χρόνο εισαγωγής στο μητρώο μέχρι ένα μικρό διάστημα μετά τον τοκετό και ανιχνεύουν μείζονα περιστατικά τερατογένεσης. Όμως ακόμη και τα μητρώα έχουν σημαντικούς περιορισμούς, όπως περιορισμένο δείγμα, αδυναμία ελέγχου του πληθυσμού και εξαιρετικά περιορισμένη παρακολούθηση σε βάθος χρόνου. Επίσης αυτές οι μελέτες περιπλέκονται από την παρουσία συγχυτικών παραγόντων, όπως το κάπνισμα, η κατανάλωση οινοπνεύματος, αλλά και η χρήση φυλλικού οξέος κατά την κύηση.

Η κλασική ταξινόμηση των πέντε κατηγοριών, η οποία είναι υπεραπλουστευμένη και συχνά συγχυτική έναντι της περιπλοκότητας και της ασάφειας της τελικής επιλογής, έχει οδηγήσει στην εξεύρεση εναλλακτικών μεθόδων εκτίμησης των κινδύνων χορήγησης φαρμάκων κατά την κύηση. Η ευρύτερη συνεργασία των ρυθμιστικών αρχών παγκοσμίως είναι αναγκαία. Ήδη από τον

Δεκέμβριο του 2014, ο FDA δημοσιοποίησε την εφαρμογή της νέας οδηγίας ταξινόμησης φαρμάκων κατά την κύηση και τον θηλασμό (New Pregnancy and Lactation Labelling Rule, PLLR),[6] η οποία τέθηκε σε εφαρμογή για όλα τα νέα φάρμακα από 30 Ιουνίου 2015, και σταδιακά για φάρμακα που αδειοδοτήθηκαν από το 2001 και εντεύθεν με αναδρομική ισχύ. Η νέα αυτή ταξινόμηση βασίζεται, όπως και οι προηγούμενες, στα παραδοσιακά μητρώα κυήσεων, αλλά και στον σχεδιασμό μεγαλύτερων μελετών κοόρτης, των βάσεων δεδομένων από τις αστικές διεκδικήσεις ατόμων τα οποία υπέστησαν βλάβη, και στην ευρύτερη συνεργασία των εμπλεκόμενων μερών (ρυθμιστικών οργανισμών, επιστημόνων, χρηστών κ.ο.κ.). Τέλος στη νέα αυτή οδηγία εντάσσεται και μια νέα παράμετρος, η οποία αφορά στην επίδραση των φαρμάκων στο αναπαραγωγικό δυναμικό γυναικών και ανδρών.

Το τοπίο στη χρήση φαρμάκων στην κύηση αλλάζει σημαντικά, μετά από τη συσσώρευση των ερευνητικών στοιχείων που δείχνουν ότι οι κίνδυνοι από τη χρήση φαρμάκων στην κύηση αλλά και στη γαλουχία έχουν μάλλον υπερτιμηθεί, ενώ παράλληλα οι διάφορες νόσοι αλλά και νοσογόνες καταστάσεις είναι δυνατόν να έχουν πολλαπλάσιες δυσμενείς επιπτώσεις τόσο στις μητέρες όσο και στα παιδιά τους.[3,7] Η σύγχρονη θεραπευτική κατά τη διάρκεια της κύησης βασίζεται σε μια ολοκληρωμένη εκτίμηση κινδύνου. Οι γονείς απαιτείται να έχουν ενεργό ρόλο στην τελική απόφαση, βοηθούμενοι από σαφείς και κατανοητές πληροφορίες εκτίμησης οφέλους-κόστους από τους θεράποντες ιατρούς τους.

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Review
Ανασκόπηση

Pharmacological agents under research for the maintenance treatment in bipolar disorder

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The treatment of bipolar disorder is a current challenge for clinicians and despite progress in psychopharmacology, options remain limited and results are often unsatisfactory. Current research focuses on finding new pharmaceutical agents for all phases of bipolar disorder, i.e. mania, bipolar depression and maintenance. Particularly, relapse prevention and long-term stabilization is a major therapeutic target. Combination treatment and polypharmacy are the most common choices concerning relapse prevention. Furthermore, during maintenance phase patients often experience residual mood symptoms, cognitive deficits and functional decline, which altogether illustrate the inadequate effectiveness of existing treatments and the need for new, targeted, effective and safe treatments for bipolar disorder. This review focuses on active agents for maintenance treatment in bipolar disorder investigated during the last 5 years. The compounds under investigation have been tried or tested either as monotherapy or as an add-on treatment in clinical trials that have progressed up to phase 3 or in preclinical models of bipolar disorder. While awaiting the completion of many ongoing studies, the results so far indicate that paliperidone and pregabalin may have a position in the maintenance treatment of bipolar disorder. Additionally, dextromethorphan, which acts primarily as a NMDA antagonist, may be an interesting compound for further study. However, results on memantine, another NMDA antagonist, were not encouraging. The effects of omega-3 fatty acids and cytidine were not superior to placebo, although they both have neurotrophic and neuroprotective properties. Eslicarbazepine, which has antiepileptic action, provided some evidence of efficacy as monotherapy. Regarding preclinical studies in experimental models, the pharmacological agents under investigation seem to follow the neurobiological pathways related to mechanism of action of lithium, which is still the "golden standard" for preventing recurrence in bipolar disorder. Major therapeutic targets are synthetic glucose kinase 3 (GSK-3) and the path of phosphoinositol (IMP), both probably involved in the action of lithium. Furthermore, the

role of circadian rhythms maintenance is being studied in preclinical and clinical trials investigating the efficacy and safety of compounds CK-01 and ramelteon, respectively. Research also focuses on pharmacological agents based on epigenetic changes and gene expression modulation, as the inhibitor of histone deacetylase (HDAC). Of note, the development of valid and reliable experimental models for bipolar disorder, which currently remains quite controversial, will contribute to the understanding of the pathogenic mechanisms and the development of new effective treatments. Improving methodology aspects of clinical trials, such as diagnosis, clinical heterogeneity, monitoring time, gender differences and comorbidities, may promote research. Current studies seem promising for the development of novel pharmacological agents in the near future, although there are methodological limitations in the search for the maintenance treatment in bipolar disorder. New therapeutic targets include not only the already known mechanisms of action, but also novel pathophysiological pathways, probably implicated in bipolar disorder.

Key words: Bipolar disorder, maintenance treatment, novel therapeutic targets, new pharmaceutical agents.

Introduction

Bipolar disorder (BD) is a chronic disease with potentially serious negative impact on patients' functioning and characterized by recurrent episodes of mania or hypomania (BD I and II type respectively) and depression. Difficulties and clinical embarrassment regarding its treatment arise from the very nature of the disease –chronic and recurrent– and other clinical characteristics, such as heterogeneity and frequent comorbidity with other mental disorders (personality disorders, substance abuse, anxiety disorders).[1]

BD treatment is a challenge for modern clinician and despite progress in psychopharmacology, options remain limited and results are often unsatisfactory. Current research focuses on finding new pharmaceutical agents for all phases of BD, i.e., antimanic, antidepressive and maintenance treatment. Especially, relapse prevention and long-term stability is a major therapeutic goal as in many cases the disorder is resistant to all first line mood-stabilizing drugs available. Augmentation strategies and polypharmacy are the most common choices for relapse prevention,[2] although it is postulated that polypharmacy does not significantly improve prognosis concerning symptom chronicity and functional impairment.[3] Moreover, patients under maintenance therapy that do not exhibit mood episode, often suffer from residual mood symptoms,[4] cognitive decline[5] and poor psychosocial functioning.[6] All the above mentioned problems concerning BD treatment demonstrate the insufficient effectiveness of existing treatments –at least for a large proportion of patients– and the need for new, targeted, effective and safe treatments that will enrich the pharmaceutical armamentarium for the complete remission of symptoms and better stabilization of BD patients. This review studied all pharmaceutical agents that have been tested, both in a clinical and a preclinical level, as potential effective maintenance treatment options.

Material and method

This review focuses on new pharmacological agents tested as BD maintenance treatment, from experimental models until phase 3 clinical trials during the last 5 years, i.e. from 2010 till April 2015. The identification of preclinical and clinical studies was conducted using databases of NIH (National Institutes of Health; http://www.clinicaltrials.gov/), EMA (European Medicines Agency; https://www.clinicaltrialsregister.eu/ctr-search/search) and WHO (World Health Organization International Clinical Registry Platform; http://apps.who.int/trialsearch). Moreover, articles from PubMed and PLOS ONE were taken into account in order to identify relevant preclinical studies and open trials. Concerning selection

criteria, compounds or pharmacological agents tested in children, adolescents or the elderly (>65 years) with BD were excluded from our study. Likewise, studies that focused exclusively on the treatment of bipolar depression, manic episode or cognitive deficits or comorbidity in BD patients, were not included. Active compounds that had progressed to phase 4 were not included in this review. The clinical trials included in this review were either completed or ongoing or were recently (from 2014 onwards) terminated for financial reasons, though they might seem promising. Pharmacological agents were further determined based on the current study phase, the type of expected therapeutic approach (monotherapy or adjunctive treatment), their mechanism of action and existing results. Regarding preclinical trials, given the lack of reliable experimental animal model for BD, only those who reported efficacy in both models of mania and depression were included in this review.

Clinical trials for maintenance treatment in BD

Our search revealed 9 completed studies (with or without announced results) and 9 ongoing studies for a total of 15 pharmacological agents tested from phase 1 to 3.

Completed studies

Seven out of 9 completed studies had reported results, 3 with favorable clinical efficacy and one with positive results for tolerability and safety, one with some evidence for efficacy, 2 did not show any significant effect, while for the remaining 2 results had not been announced at the time of writing this report (table 1).

Dextromethorphan

Dextromethorphan is widely used as a cough suppressant, but has been reported to have neuroprotective effects on dopaminergic neurons and anti-inflammation properties associated with neuronal degeneration in both experimental models and clinical trials.[7,8] In addition, as it shares pharmacodynamic properties similar to ketamine,[9] mainly as a NMDA-receptor antagonist and σ1 and σ2 opioid-receptor agonist, its possible use as antidepressant is under investigation.[9] In a recent phase 3 trial, dextromethorphan was studied for 12 weeks as an adjunctive treatment (30 mg and 60 mg) to 309 BD patients who had been receiving valproate, while 123 healthy subjects were used as controls (receiving valproate and placebo).[10] The study showed good efficacy for those taking dextromethorphan as an add-on treatment in terms of measuring YMRS (Young Mania Rating Scale) and HDRS (Hamilton Depression Rating Scale).[10] This finding encourages further research into the potential therapeutic role of dextromethorphan in maintenance treatment of BD.

Pregabalin

The use of pregabalin as an antiepileptic drug and in the treatment of generalized anxiety disorder and neuropathic pain is known. Pregabalin's chemical structure is considered to be analogous to GABA and binds with the a-2δ subunit of the voltage-dependent calcium channel. The possible use of pregabalin as an add-on treatment was addressed in an open label study[11] in 58 refractory BD patients. In 41% of patients (acute responders) that were administered an average dose of 72±69 mg/d, significant improvement was noticed in CGI scale (Clinical Global Impression) after two months. In these patients pregabalin demonstrated either antidepressant (29%), or antimanic (21%) or stabilizing properties (50%), while 42% continued to receive it after 3 years.[11] These results indicate that pregabalin might have a role in maintenance therapy.

Paliperidone

Paliperidone belongs to the class of atypical antipsychotics, acting primarily as a dopamine and serotonin receptor antagonist, indicated for the treatment of schizophrenia and schizoaffective disorder. In one study,[12] bipolar patients (n=152), who had recently achieved remission taking paliperidone ER (extended release), were compared to patients treated with placebo after the recession (n=148) in the maintenance phase. The results of this study at 41 months follow-up assessment con-

Table 1. Completed studies of pharmacological agents under research for maintenance treatment in bipolar disorder.

Pharmacological agent/Compound	Study identifier	Phase	Treatment as	Main mechanism of action	Results
Dextromethorphan	NCT01188265	Phase 3	Add-on	Antagonism of NMDA receptors, agonism of σ1 and σ2 opioid receptors	Significant improvement compared to placebo in YMRS and HDRS
Pregabalin	Open Label	Phase 2	Add-on	Binds to the a-2-delta subunit of voltage-dependent calcium channel	Improvement in CGI-BP scale
Paliperidone	NCT00490971	Phase 3	Monotherapy	Antagonism of dopamine and serotonin receptors	Significant improvement compared to placebo for prevention of manic but not depressive episodes
Eslicarbazepine	NCT01825837	Phase 2	Monotherapy	Blockade of voltage-gated sodium channels	No significant differences in CGI-BP or relapse prevention. Evidence of efficacy in stabilizing after manic episode
Memantine	NCT01188148	Phase 2–3	Add-on	Antagonism of NMDA receptors	No significant differences compared to placebo in YMRS and HDRS
Cytidine and omega 3 fatty acids	NCT00854737	Phase 2	Add-on	Neurotrophic/ neuroprotective action	Not superior to placebo
Cariprazine	NCT01059539	Phase 3	Monotherapy	Partial agonism of D2, D3 receptors	Efficacy in safety and tolerability
Taurine	NCT00217165	Phase 2	Add-on	Antioxidant activity, cell membrane stabilization, calcium signalling modulation	No results available
Antibodies to digoxin	NCT00550576	Phase 2	Add-on	Action against endogenous digitalis-like compounds	No results available

CGI-BP: Clinical Global Impression – Bipolar Version; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale

cerning relapse for any major mood episode (depressive or manic) showed that the average time to relapse in subjects who received paliperidone was 558 days compared to 283 days for those receiving placebo. However, this finding was statistically significant regarding the prevention of manic but not depressive episodes.[12]

Eslicarbazepine

Eslicarbazepine, chemically similar to oxcarbazepine, is used in the treatment of partial seizures by blocking voltage-gated sodium channels. Its possible role as a mood stabilizer was recently examined in a phase 2 study in 85 BD patients who had

recently achieved remission after manic episode. Patients were randomized into three groups receiving eslicarbazepine as monotherapy at doses of 300 mg, 900 mg and 1800 mg respectively, and were assessed for six months. The results of this study did not show statistically significant efficacy for any of the three groups in terms of clinical improvement (as measured by the Clinical Global impression scale) or relapse prevention (as measured by the number of subjects who developed manic or depressive episode). However, secondary efficacy measurements showed that eslicarbazepine in a dosage of 300 mg to 900 mg was significantly more effective than placebo in achieving normothymia after manic episode. Eslicarbazepine was also found generally safe and well tolerated.[13]

Memantine

Memantine is indicated for the treatment of moderate to severe Alzheimer's disease, by acting as an NMDA-receptor antagonist. Although there is some data indicating a possible synergic role of memantine as mood stabilizer, possibly in the context of neuroprotection/neurogenesis,[14] as both antidepressant[15] and antimanic[16] agent, there has been no strong evidence in favor of these hypothetically therapeutic actions. In a 12 week, phase 2–3, double-blind study, memantine was compared to placebo as an add-on treatment in patients taking valproate without any significant difference in terms of efficacy.[17] However, studies of memantine continue to be conducted with the expectation of more favorable results.[18]

Cytidine and omega 3 fatty acids

Cytidine and omega 3 fatty acids as natural dietary supplements have neurotrophic and neuroprotective action. Their role in BD is not clear, with ambiguous evidence concerning efficacy.[19–21] In a four month, double-blind study, groups of BD patients receiving as an add-on treatment: (a) omega 3 fatty acids and (b) omega 3 fatty acids and cytidine were compared with a group receiving placebo in terms of relapse prevention. Among the compared groups no difference was noticed either in preventing relapse or improving symptoms as measured by scales of mania and depression.[22]

Cariprazine

Cariprazine is a new atypical antipsychotic with a novel pharmacological profile, acting as a D2, D3 receptor partial agonist. Studies have shown good tolerability and safety but also effectiveness in the treatment of manic, mixed episode,[23,24] while there are positive indications for bipolar depression.[25] A two week, phase 3 study in 402 BD patients was conducted in terms of examining safety and tolerance. This study showed promising results for its administration in longer term, as main side effect was akathisia (32.6%), but this resulted in discontinuation in only 4.7% of people who presented it.[26]

Taurine

Taurine is an amino-acid found in the human brain, showing antioxidant activity with a possible role in cell membrane stabilization and calcium signaling modulation. It potentially presents antidepressant activity, as shown by testing in experimental models,[27] and antiepileptic properties.[28] Its possible place in BD maintenance treatment is investigated in a phase 2 trial, but no results have yet been reported.

Specific digoxin antibodies (FAB)

As endogenous digitalis-like central nervous system compounds are involved in the pathogenesis of mood disorders,[29] a phase 2 trial has examined the safety and efficacy profile of specific digoxin antibodies (FAB) in BD patients, without any announced outcome measures as yet.

Ongoing clinical trials for maintenance treatment in BD

Our search revealed 9 clinical ongoing trials, recruiting or active (not recruiting - analysis phase) investigating 6 pharmacological agents (table 2) that had not announced results at the time of writing this report.

Inositol Hexaphosphate (IP6)

IP6 is involved in the intracellular system of second messenger phosphatidylinositol, with potential antidepressant role in bipolar depression, as small studies indicate.[30] In an ongoing phase 1 trial, IP6 will be

Table 2. Ongoing clinical trials for maintenance treatment in bipolar disorder.

Pharmacological agent/Compound	Study identifier	Phase	Treatment as	Main mechanism of action	Results (to be announced)
Inositol Hexaphosphate (IP6)	NCT02081287	Phase 1	Add-on	Neuroprotective action	November 2015
ELND005 (Scyllo-Inositol)	NCT01674010	Phase 2	Add-on	Blockade of Amyloid-beta (Aβ) development	Recently terminated
Ramelteon	NCT01467713	Phase 3	Add-on	Agonist of MT1 and MT2 receptors	Recently terminated
Lurasidone	NCT01358357 NCT01575561 NCT01986114	Phase 3	Add-on Monotherapy	Antagonism of dopamine, serotonin and noradrenalin receptors	April 2015 July 2015 September 2017
Asenapine	NCT01396291	Phase 3	Monotherapy	Antagonism of D2, 5-HT_2A receptors	June 2015
Aripiprazole	NCT01567527 NCT01710709	Phase 3	Monotherapy	Partial agonist of D2, 5-HT_2A receptors	April 2017 February 2016

studied for safety and effectiveness as an adjunctive treatment to lithium and will be compared with lamotrigine regarding their antidepressant and stabilizing properties.

ELND005 (Scyllo - Inositol)

ELND005 is an experimental compound for Alzheimer's disease treatment as it appears to act as an amyloid-β aggregation inhibitor. A double-blind phase 2 clinical trial for ELND005 as an add-on treatment in BD maintenance therapy was recently stopped by the sponsoring company for financial reasons.

Ramelteon

Ramelteon binds to melatonergic receptors MT1 and MT2 and beyond its use as hypnotic, it can play a role in the regulation of circadian rhythms, whose maintenance is particularly important for preventing recurrence of BD episodes. While a phase 4 study announced efficacy of ramelteon as maintenance therapy,[31] a phase 3 trial for its sublingual form, aiming at alternative ways of administration, was recently suspended due to financial reasons.

Lurasidone

Lurasidone is a new atypical antipsychotic that has been approved for the treatment of bipolar depression, either as monotherapy or as an add-on treatment.[32] Regarding relapse prevention, lurasidone is studied in three phase 3 trials (table 2), a double blind, one open-label as an add-on treatment and one open-label as monotherapy for 28, 12 and 52 weeks respectively. Results of these studies are expected.

Asenapine

Asenapine is an atypical antipsychotic for the treatment of schizophrenia and manic/mixed episode. Besides bipolar depression,[33] asenapine is studied as monotherapy in a double-blind trial, compared to placebo for mood episode prevention.

Aripiprazole

Aripiprazole is used as monotherapy or adjunctive treatment for manic/mixed episode and maintenance treatment, while it is controversial whether it is effective in bipolar depression.[34–36] For the time being, two phase 3 trials are investigating the use of

long acting injectable aripiprazole for 52 weeks for BD maintenance therapy.

Preclinical studies for maintenance therapy for bipolar disorder

Our search for the last 5 years found 5 eligible studies corresponding to equal number of pharmacological agents (table 3), that showed efficacy in experimental models of both mania and depression. This inclusion criteria was considered more accurate, since there is no valid and reliable animal model of BD, due to difficulty to reflect the phenotype of switching symptoms of mania and depression at the same model.[37]

CK01

The compound CK01 inhibits the function of the casein kinase 1 (CK1) ε/δ, which is believed to be involved in the modulation of the molecular clock and therefore circadian rythm.[38] CLOCK mice, carry a mutation in one of the essential proteins associated with maintaining circadian rhythm and present significant disruption of it along with a behavioral profile resembling a phenotype similar to human mania. In one study, CK01 was administered to CLOCK mice and then compared to lithium's action. Results showed reversal of anxiety-hyperactivity behavior (as lithium) and partial reversal of the phenotype of depression forced-swim test model.[39] The above results suggest that pharmaceutical agents that inhibit CK1, may have therapeutic value for BD.

Ebselen

Ebselen is a compound with significant antioxidant properties that inhibits monophosphatase inositol (IMP). It was observed that it mimics the action of lithium, probably because via the common neurobiological pathway of inositol recycling inhibition, exhibiting similar efficacy in preclinical stage.[40] It has been found to be effective in both depression[41] and

Table 3. Preclinical trials for maintenance treatment in bipolar disorder.

Compound	Animal model Mania/Depression	Mechanism of action	Results Mania/Depression model
CK01	CLOCK mice	CK1 ε/δ inhibition	Reversal of stress behavior - hyperactivity/partial reversal of depression phenotype
Ebselen	Model: amphetamine-induced hyperactivity/forced swim test and tail suspension test in mice	IMP inhibition	Similar to the action of lithium: Reduction of the observed behavior of rearing and hyperactivity/reduction of immobility time
Peptide TAT – KLCpCDK	Model: amphetamine-induced hyperactivity/forced swim test and tail suspension test in mice	GSK-3 inhibition of KLC2 phosphorylation and AMPA glutamate receptors modulation	Similar to the action of lithium: Reduction of the observed behavior of amphetamine-induced hyperactivity/reduction of immobility time
Cpd-60	Model: amphetamine-induced hyperactivity/forced swim test in mice	HDAC ½ inhibition	Reduction of the observed behavior of amphetamine-induced hyperactivity/reduction of immobility time
Sodium butyrate (SB)	Model: AMPH-induced hyperactivity in Wistar rats/maternal deprivation and chronic mild stress	HDAC inhibition	Reversal of mania/depression phenotype respectively

CK: Casein kinase, IMP: Monophosphatase inositol, GSK-3: glycogen synthase kinase-3, KLC-2: kinase light chain 2, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole propionate, HDAC: Histone Deacetylase

mania[40] models, and therefore a candidate agent for further study in treating BD.

Peptide TAT – KLCpCDK

This peptide has been found to have lithium-like properties, inhibiting glycogen synthase-3 kinase (GSK-3), while additionally shows effectiveness in both models of depression and mania.[42] Although results of this study were announced in 2010, there have not been since then, known to us at least, further clinical trials for this agent in BD.

Cpd-60

Cpd-60 acts as a selective 1/2 histone deacetylase (HDAC 1/2) inhibitor, modulating chromatin and gene expression in mouse brains. Evidence of its efficacy has been found in both mania and depression models.[43] Inhibition of HDAC may be a candidate target for the development of epigenetic acting agents that would have a therapeutic role in BD.

Sodium Butyrate (SB)

This compound, similarly to Cpd-60, inhibits HDAC and simultaneously exhibits neurotrophic activity. SB administration in experimental models of mania[44,45] and depression[44,46] resulted in amelioration of behavioral patterns, indicating a possible mood stabilizing role.

Current limitations and prospects in maintenance treatment of BD

The need to develop new treatments for BD is beyond any doubt. There are therapeutic difficulties in BD, especially in preventing depressive episodes or depressive residual symptoms or treating BD II in the long-term.[47] Lithium may be the golden option for relapse prevention, but, as noted above, a proportion of BD patients will not respond (non-responders)[48] or be fully protected, regarding mixed or rapid-cycling type, and often will present side effects,[49] which impede therapeutic process. Moreover, many patients are treatment resistant,[50] presenting with residual symptoms during maintenance phase[51] and therefore ongoing treatment is considered inadequate. The phenomenon of polypharmacy[2] is also frequent in order to achieve stabilization and treat residual symptoms. Finally, new pharmaceutical agents which are developed based on the mechanism of lithium action or other pathophysiological pathways may contribute to the understanding of the underlying neurobiological substrates of BD.[52]

From this review it appears that three active compounds (dextromethorphan, pregabalin, paliperidone) and possibly eslicarbazepine have shown some positive evidence for BD maintenance therapy. Considering, however, the methodology of these and other ongoing trials, there are marked differences in the definition of maintenance therapy, the required time for long-term prophylaxis and how efficacy of each intervention is evaluated. Measuring clinical levels of functioning or residual symptoms (mania or depression) does not seem to ensure long-term prevention. Regarding study design, it may be preferable to use days to relapse (for any major mood episode) or the number of individuals who will finally relapse as primary outcome measures and the longest, possible, follow-up time period for which a prophylactic treatment will be considered adequate. Methodological issues, such as diagnosis, clinical heterogeneity, gender differences and comorbidity,[53] should also be addressed in order to promote research.[52] Finally, regarding preclinical trials, there are important limitations in developing a reliable, valid BD model that will present both the pole of mania and depression in a single behavioral phenotype.[37]

Based on the above concerning studies design, paliperidone seems to have favorable profile for further study as a mood stabilizer, although, for the moment, it seems to be effective only in the prevention of manic episodes. Cariprazine is another antipsychotic that presents with a novel mechanism of action and has shown good tolerability and safety. Results on the efficacy of cariprazine in maintenance treatment are expected, as well as from other atypical antipsychotics, namely lurasidone, asenapine and long-acting aripiprazole. Study results on the efficacy of NMDA receptors inhibitors, dextromethorphan and memantine, are so far mixed, although there is preliminary positive evidence for dextromethorphan. Pregabalin

and eslicarbazepine are anticonvulsants with prospects of further study in BD maintenance treatment. Trials of pharmaceutical agents with neuroprotective and/or neurotrophic properties, such as omega-3 fatty acids and cytidine, did not reveal positive results. Studies on the therapeutic benefit of modulating circadian rhythms in both experimental models and clinical trials, with CK01 and ramelteon respectively, have yielded encouraging results. In preclinical level, neurobiological pathways of GSK-3 and IMP inhibition, both related to the therapeutic effects of lithium, are known and important targets for the development of pharmaceutical agents for BD.[52,54] Pharmacological agents based on epigenetic changes and gene expression modulation, such as the inhibitor of HDAC, are earning more ground in modern research for BD.[52,54,55]

Φαρμακολογικοί παράγοντες υπό μελέτη για τη θεραπεία συντήρησης στη διπολική διαταραχή

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Η θεραπεία της διπολικής διαταραχής αποτελεί πρόκληση για τον σύγχρονο κλινικό και, παρά την πρόοδο της ψυχοφαρμακολογίας, οι επιλογές παραμένουν περιορισμένες και τα αποτελέσματα συχνά μη ικανοποιητικά. Η σύγχρονη έρευνα επικεντρώνεται στην ανεύρεση νέων φαρμακευτικών παραγόντων για όλες τις φάσεις της διπολικής διαταραχής, για την αντιμετώπιση μανιακών και καταθλιπτικών επεισοδίων και τη θεραπεία συντήρησης. Ιδιαίτερα η πρόληψη των υποτροπών και η μακροπρόθεσμη σταθεροποίηση συνιστά μείζονα θεραπευτικό στόχο. Οι συνδυαστικές θεραπείες και η πολυφαρμακία αποτελούν την πλέον συχνή τακτική επιλογή στη πρόληψη των υποτροπών. Επιπλέον, στη φάση συντήρησης οι ασθενείς βιώνουν συχνά υπολειπόμενα συμπτώματα από τη διάθεση, παρουσιάζουν γνωστικά ελλείμματα και λειτουργική έκπτωση, κάτι που καταδεικνύει τη μη επαρκή αποτελεσματικότητα των υπαρχουσών θεραπειών και την ανάγκη για νέες, στοχευμένες, αποτελεσματικές και ασφαλείς θεραπείες για τη διπολική διαταραχή. Η παρούσα ανασκόπηση εστιάζει σε δραστικές ουσίες για τη θεραπεία συντήρησης που διερευνώνται την τελευταία 5ετία. Οι υπό έρευνα ουσίες έχουν δοκιμαστεί ή δοκιμάζονται είτε ως μονοθεραπεία είτε ως θεραπεία ενίσχυσης σε κλινικές δοκιμές που έχουν προχωρήσει έως την φάση 3 ή σε προκλινικά μοντέλα διπολικής διαταραχής. Ενώ αναμένεται η ολοκλήρωση πολλών τρεχουσών μελετών, τα μέχρι τώρα αποτελέσματα δείχνουν ότι η παλιπεριδόνη και η πρεγκαμπαλίνη ίσως έχουν θέση στη θεραπεία συντήρησης της διπολικής διαταραχής. Επιπρόσθετα, η δεξτρομεθορφάνη, που δρα κυρίως ως NMDA ανταγωνιστής, παρουσιάζεται ως ενδιαφέρουσα ουσία για περαιτέρω μελέτη. Ωστόσο η μεμαντίνη που είναι επίσης NMDA ανταγωνιστής δεν έχει δώσει ενθαρρυντικά αποτελέσματα. Από την άλλη πλευρά, οι μέχρι τώρα δοκιμές ω-3 λιπαρά οξέα και κυτιδίνη δεν έδειξαν ανώτερη αποτελεσματικότητα σε σχέση με το εικονικό φάρμακο, παρόλο που έχουν τόσο νευροτροφικές όσο και νευροπροστατευτικές ιδιότητες. Η αντιεπιλη-

πτικής δράσης εσλικαρβαζεπίνη είχε κάποιες ενδείξεις αποτελεσματικότητας ως μονοθεραπεία. Όσον αφορά στις μελέτες σε προκλινικά, πειραματικά μοντέλα, οι υπό έρευνα ουσίες φαίνεται να ακολουθούν το νευροβιολογικό μονοπάτι του λιθίου, που εξακολουθεί να είναι η «χρυσή επιλογή» για την πρόληψη υποτροπών στη διπολική διαταραχή. Κύριοι θεραπευτικοί στόχοι είναι η συνθετική κινάση της γλυκόζης 3 (GSK-3) και το μονοπάτι της φωσφοϊνοσιτόλης (IMP), που υποστηρίζεται ότι εμπλέκονται στη δράση του λιθίου. Επιπλέον, η διατήρηση των κιρκάδιων ρυθμών εξετάζεται σε προκλινικές και κλινικές μελέτες με τη διερεύνηση της αποτελεσματικότητας και ασφάλειας των ουσιών CK-01 και ραμελτεόνης αντίστοιχα. Η έρευνα εστιάζει επίσης σε φαρμακευτικά μόρια που σχετίζονται με επιγεννητικές μεταβολές ή τη ρύθμιση της γονιδιακής έκφρασης, όπως η ιστόνη της δεακετυλάσης (HDAC). Θα πρέπει επίσης να επισημανθεί ότι η ανάπτυξη έγκυρων και αξιόπιστων πειραματικών μοντέλων διπολικής διαταραχής, που προς το παρόν παραμένει αρκετά αμφιλεγόμενη, θα συμβάλει στην κατανόηση των παθογενετικών μηχανισμών της αλλά και στην ανεύρεση κατάλληλων και αποτελεσματικών θεραπειών. Επίσης, η βελτίωση των μελετών σε μεθοδολογικά ζητήματα όπως η διάγνωση, η κλινική ετερογένεια, ο χρόνος παρακολούθησης, οι διαφορές ανάμεσα στα φύλα και η συννοσηρότητα, μπορεί να προαγάγουν την έρευνα. Οι τρέχουσες μελέτες αφήνουν περιθώρια για την ανάπτυξη νέων δραστικών ουσιών στο άμεσο μέλλον, μολονότι υπάρχουν μεθοδολογικοί περιορισμοί στην έρευνα για τη θεραπεία συντήρησης στη διπολική διαταραχή. Οι νέοι θεραπευτικοί στόχοι περιλαμβάνουν όχι μόνο τους ήδη γνωστούς μηχανισμούς δράσης αλλά και νέα παθοφυσιολογικά μονοπάτια που πιθανώς εμπλέκονται στη διπολική διαταραχή.

Λέξεις ευρετηρίου: Διπολική διαταραχή, θεραπεία συντήρησης, νέοι θεραπευτικοί στόχοι, νέοι φαρμακολογικοί παράγοντες.

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Special article
Ειδικό άρθρο

Mental health services commissioning and provision: Lessons from the UK?

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The commissioning and provision of healthcare, including mental health services, must be consistent with ethical principles – which can be summarised as being "fair", irrespective of the method chosen to deliver care. They must also provide value to both patients and society in general. Value may be defined as the ratio of patient health outcomes to the cost of service across the whole care pathway. Particularly in difficult times, it is essential to keep an open mind as to how this might be best achieved. National and regional policies will necessarily vary as they reflect diverse local histories, cultures, needs and preferences. As systems of commissioning and delivering mental health care vary from country to country, there is the opportunity to learn from others. In the future international comparisons may help identify policies and systems that can work across nations and regions. However a persistent problem is the lack of clear evidence over cost and quality delivered by different local or national models. The best informed economists, when asked about the international evidence do not provide clear answers, stating that it depends how you measure cost and quality, the national governance model and the level of resources. The UK has a centrally managed system funded by general taxation, known as the National Health Service (NHS). Since 2010, the UK's new Coalition* government has responded by further reforming the system of purchasing and providing NHS services – aiming to strengthen choice and competition between providers on the basis of quality and outcomes as well as price. Although the present coalition government's intention is to maintain a tax-funded system, free at the point of delivery, introducing market-style purchasing and provider-side reforms to encompass all of these bring new risks, whilst not pursuing reforms of a system in crisis is also seen to carry risks. Competition might bring efficiency, but may weaken cooperation between providers, and transparency too. On the other hand, it is hard to implement necessary governance and control without worsening bureaucracy and inefficiency. The pursuit of market efficiencies has been particularly contentious in men-

*Since May 2015, following general elections, the UK has a Conservative government.

tal health care, where many professionals are defensive about the risks to vulnerable patients and to traditional ways of professional working. Developments and debates in the UK may be instructive for others. We conclude this paper with a set of questions that may help inform debate and evaluation of mental health services internationally.

Key words: Mental-health services, commissioning services, provision of services, UK.

Introduction

The ethical foundations of the modern state rest with respecting, protecting and enhancing the liberty of citizens, and negotiating such social arrangements as protect and advance the interests of the most vulnerable in society.[1] The ethical foundations of professionalism in medicine are respect for patient autonomy, promotion of patient welfare and social justice.[2] The commissioning and provision of health services, including mental health services, must be consistent with these ethical principles. Because resources are always finite and must be prioritised, ethical healthcare services must also deliver value to patients and society, defined by the Harvard economist Porter[3] as the ratio of patient outcomes divided by cost of service across the whole care pathway.

Every country should have adequate national mental health policy and service provision.[4] Mental health services must provide for the population as a whole, but also ensure that the human rights and welfare of the most vulnerable, such as those with severe mental illness, are safeguarded and enhanced.[5] However the mental health of the population is affected by factors beyond mental health practice, particularly by levels of inequality in the population.[6] Psychiatrists are now seeing the fall out of the international debt crisis roll through society, and affect the most vulnerable in the population. This is inevitably placing significant extra demands on national systems of mental health care.

Systems of commissioning and delivering mental health care vary from country to country, bringing the possibility of learning from others. Particularly in difficult times, with major challenges in meeting levels of need, it is essential to keep an open mind as to how things might be done differently. In the current harsh economic era, that often means how to provide more with less – how to successfully achieve service reform, to bring greater efficiency and effectiveness. In the field of public healthcare this often requires a fresh, "business-like" approach, which unfortunately raises the spectre of unfair treatment of vulnerable people through unrestrained markets. On the other hand, as evidenced by well-documented scandals in state-run mental health services in the UK and elsewhere, such provision is by no means an absolute guarantor of the welfare of the vulnerable.

In fact, greater efficiency and effectiveness require strengthened systems of governance to ensure fair provision of healthcare. Daniels[7] suggests that the hallmarks of fairness are equity, efficiency and accountability. Health equity reflects all policies affecting public health, not just health policies, as well as financial barriers to equitable healthcare access, non-financial barriers to access and comprehensiveness of benefits. Efficiency includes quality improvement and administrative competency. Democratic accountability requires empowerment, and patient and provider autonomy. Such hallmarks provide a possible way of evaluating health services irrespective of specific purchasing arrangements and support reasoned debate and implementation arrangements which deliver value and fairness in mental healthcare.

The challenge

A study by the European Union and the World Health Organisation compared mental health care systems across Europe.[4] The report's conclusion that the best policies and practices could be found in the English National Health Service (NHS) was based on data provided by central government departments, although outcomes or cost-effectiveness were not assessed. England has among the highest rates of mental ill-health and other social problems in Europe,[6] and spends a larger proportion of its health budget on mental health than any other country

in the continent.[8] At the time of the EU/WHO study there had been significant increase in spending on mental health services. While the report highlighted the strengths of the English system, some senior psychiatrists have expressed concerns about the actual quality of assessment and care that patients receive.[9–10]

The UK has a centrally managed system funded by general taxation, known as the National Health Service (NHS). Funding has doubled every decade since its foundation in 1948, irrespective of political party in power, with the exception of the decade to 2010, when the total investment trebled. In the economic boom years, government and commercial healthcare spending and investment in many countries was supported by large scale borrowing. Such funding has depended on public borrowing and tax receipts, including in the UK high tax receipts from the strong banking and finance sector.

Significant investment has been channelled into UK mental healthcare, including novel programmes of community care and psychological treatments focussed on priorities such as fitness to work.[11] Of the increase in adult mental health and social care in England between 2001 and 2009, 83% was commissioned by the NHS, but over 30% was provided by independent organisations.[12] The UK saw many new modern hospitals and community homes built, and new teams and service models launched, from which mental health patients greatly benefited. However the debt crisis is now bringing new constraints in health spending, and sharp reductions in social care expenditure, with mental health patients amongst the vulnerable people most affected. At the present time public, commercial and charitable healthcare providers are affected adversely, with some providers struggling to survive. The authors are aware of an increasing number of quality scandals and bankruptcies in the UK healthcare sector. These strains are compounded by increasing healthcare demands from the impact of unemployment, and increasing numbers of elderly – essentially the ratio of sick people to tax payers is growing.

Since 2010, the UK's new Coalition government has responded by further reforming the system of purchasing and providing NHS services – aiming to strengthen choice and competition between providers on the basis of quality and outcomes as well as price.[13] This pursuit of market efficiencies has been particularly contentious in mental health care, where many professionals are defensive about the risks to vulnerable patients and to traditional professional ways of working. Whilst there is some evidence that forms of commissioning in primary care, as proposed by the Government, can reduce costs, little of this relates to mental health, and such changes may bring other risks to patients.[14]

The debate

Different systems of governance, such as in state, commercial and charity sectors have different strengths and weaknesses. Introducing market-style purchasing and provider-side reforms to encompass all of these bring new risks, whilst not pursuing reforms of a system in crisis is also seen to carry risks. Competition might bring efficiency but is likely to weaken co-operation between providers, and transparency too. On the other hand it is hard to implement necessary governance and control without worsening bureaucracy and inefficiency.

Following de-institutionalisation programmes, the reduction of UK state in-patient beds, provision of community care homes and specialist housing and support for people with chronic mental health problems, the elderly and people with intellectual disabilities are now largely independent of the state. Several areas of specialist hospital care, ranging from longer-term forensic units to eating disorders to brain injury, are now mostly provided for by commercial organisations, and this is reflected in data on compulsory detentions to independent hospitals.[15] Some national commercial groups running psychiatric hospitals and care homes are now larger than the local, catchment area based, NHS providers in which, for the time being, most psychiatric in-patient beds and professional multi-disciplinary teams remain. The income of the commercial sector is largely derived from NHS commissioners and local government authorities. Many are uncomfortable with the

large profits made by some private equity owners in this market.

Some argue that the UK reforms have not gone far enough as they do not allow real competition, based on a choice of quality services by empowered patients and purchasers of services. Current debates in the UK[16–20] demonstrate the complex arguments in gauging the risks and benefits of market approaches to healthcare, and the strong feelings of psychiatrists who have given their professional lives to public service.

Opponents of private care typically quote experience in the United States[18–20] and cite quality and financial scandals in private healthcare, whilst proponents are similarly tempted to cite equally unacceptable failures in public mental health care.[21] A persistent problem is the lack of clear evidence over cost and quality delivered by different local or national models.[5] The best informed economists, when asked about the international evidence do not provide clear answers, stating that it depends how you measure cost, the national governance model and the level of resources.[22] In mental health the definition of outcomes can be difficult, as a variety of dimensions need to be assessed including prevention, patient experience, patient safety as well as symptomatic change. The complexity of this issue is evidenced by repeated delays in the UK government extending is "payment by results" programme into mental health.[23] Meanwhile examples of providers publishing comprehensive outcome data in mental health are rare.[24]

The US-based Commonwealth Foundation[25] compared seven healthcare systems in English-speaking and European countries (Australia, Canada, New Zealand, UK, US, Germany and the Netherlands). The study found that overall the US system ranked last of the seven countries – despite the fact that the US spent on healthcare more than the other countries both in absolute and relative terms. The Netherlands had the best system overall – one feature is that the Dutch system allows citizens choice between purchasers as well as providers of health services.

In the Commonwealth Foundation study the UK scored second overall – it is a less wealthy country per head of population than the Netherlands and spends significantly less on healthcare in absolute terms. However, it was assessed as best for effectiveness and appropriateness of care. On the other hand it scored worse than all others on measures of person-centred care. Furthermore the UK population as a whole was found to be 6th out of 7 in terms of long productive lives.

It could be concluded from the study that choice[26] can be effective in healthcare, that level of expenditure does not necessary determine outcomes, and that nature and quality of the health service is not the fundamental determinant of a country's population health. However more can be learnt by looking closely at the unequal benefits for different sections of the population. Whilst wealthy US citizens get some of the best healthcare anywhere, the poorer, vulnerable population in the US clearly receives worse care than most European counterparts. Such concerns are compounded with real political issues[6] –there is inequality in care but also in the burden of resourcing– in the UK 50% of the population pays 90% of total tax, 25% of which pays for the NHS.

The experience between countries of more severely ill, vulnerable patients requires further scrutiny. Roehr[27] found that for people with complex needs coordination of care was best in the UK, compared with other Anglo-Saxon and European countries, whilst the Commonwealth Fund[28] found that for sicker adults, the UK was average in terms of timely access to care and availability of records at appointment. It seems likely that different systems serve better the needs of different patient populations, for example Netherlands for the acutely sick, UK for complex long term conditions.

In reality in the UK elements of a mixed healthcare economy system of state and independent providers has been in development for at least two decades. Market reforms in acute healthcare have been supported by successive Governments – especially commercial provision of elective surgery offering a solution to long waiting times in the NHS, with elements of general practice down increasingly involved with private companies. In mental health, whilst value for money and quality from the private mental health

sector have long been questioned,[29] a diversity of state, private and voluntary mental health provision continues to develop, focussed on provision for the more severely ill and vulnerable patient populations.

Conclusion

The NHS has been in the UK a long standing social landmark strongly supported by the public and professionals including mental health professionals. Over the last 20 years the NHS has been operating more as a business organisation, in pursuit of market efficiencies and improved effectiveness. This has brought out many challenges and debates. Ultimately, the test of the method chosen to purchase and deliver health care is whether it produces "fair outcomes" for whole populations and patients.

It would be appropriate for all countries to benchmark their current or proposed commissioning systems on the following criteria:

Is the system designed to deliver fair, ethical healthcare?

Have we defined what we mean by 'outcomes' within our services?

What data do we have on which to audit this?

Do we have a balance between providers of different kinds to provide a choice to patients?

How might we move forward to close some of the gaps identified from the above mentioned questions?

What can we learn from experiences in other countries?

Ανάθεση και παροχή υπηρεσιών υγείας: Διδάγματα από το Ηνωμένο Βασίλειο (UK);

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Η ανάθεση και η παροχή υπηρεσιών υγείας, συμπεριλαμβανομένων των υπηρεσιών ψυχικής υγείας, πρέπει να συνάδουν με τις αρχές της Ηθικής και της Δεοντολογίας – οι οποίες θα μπορούσαν να συνοψιστούν ως «δίκαιες», ανεξάρτητα από την επιλεχθείσα μέθοδο παροχής φροντίδας. Επίσης, πρέπει να είναι συμφέρουσες τόσο για τους ασθενείς όσο και για την κοινωνία γενικότερα. Το «συμφέρον» θα μπορούσε να ορισθεί ως ο λόγος των αποτελεσμάτων στην υγεία των ασθενών προς το κόστος των υπηρεσιών καθόλη τη διαδικασία της φροντίδας. Ειδικά σε δύσκολους καιρούς, είναι απαραίτητη η δεκτικότητα ως προς τους τρόπους που κάτι τέτοιο μπορεί να επιτευχθεί. Σίγουρα οι εθνικές και οι περιφερειακές πολιτικές θα διαφέρουν, καθώς οι τελευταίες αντανακλούν την ιστορία, την κουλτούρα, τις ανάγκες και τις επιλογές της συγκεκριμένης περιφέρειας. Καθώς η ανάθεση και η παροχή ψυχικής φροντίδας διαφέρουν από χώρα σε χώρα, υπάρχει η δυνατότητα να μάθουμε από άλλους. Στο μέλλον οι διεθνείς συγκρίσεις μπορούν να χρησιμεύσουν στην αναγνώριση πολιτικών και συστημάτων ικανών να λειτουργήσουν διακρατικά και διατοπικά. Ένα επίμονο πρόβλημα είναι η έλλειψη σαφών στοιχείων για το οικονομικό κόστος και την ποιότητα που παρέχουν τα διάφορα τοπικά ή εθνικά συστήματα. Όταν ερωτώνται για τα διεθνή στοιχεία, οι οικονομικοί αναλυτές δεν δίνουν σαφή απάντηση, υποστηρίζοντας πως η τελευταία εξαρτάται από το πώς μετριούνται το οικονομικό κόστος, το εθνικό μοντέλο διακυβέρνησης και το ύψος των πόρων. Το Ηνωμένο Βασίλειο έχει ένα κεντρικά διαχειριζόμενο σύστημα που χρηματοδοτείται από τη γενική φορολογία, γνωστό ως Εθνικό Σύστημα Υγείας (National Health

Service). Από το 2010, ο νέος κυβερνητικός συνασπισμός του Ηνωμένου Βασιλείου προχώρησε στην περαιτέρω μεταρρύθμιση του συστήματος αγοράς και παροχής υπηρεσιών του NHS, με σκοπό την ενδυνάμωση των επιλογών και της ανταγωνιστικότητας μεταξύ των φορέων παροχής υπηρεσιών με βάση την ποιότητα, τα αποτελέσματα και το οικονομικό κόστος. Αν και η πρόθεση του κυβερνητικού συνασπισμού είναι η διατήρηση ενός συστήματος χρηματοδοτούμενου από τη φορολογία και δωρεάν στο σημείο παροχής, η εισαγωγή των πρακτικών της αγοράς στην ανάθεση υπηρεσιών και οι μεταρρυθμίσεις από την πλευρά των φορέων παροχής υπηρεσιών συνδέονται με νέους κινδύνους, ενώ η μη επιδίωξη της μεταρρύθμισης ενός συστήματος σε κρίση επίσης εγκυμονεί κινδύνους. Ο ανταγωνισμός μπορεί να αποφέρει αποδοτικότητα αλλά ενδέχεται και να αποδυναμώσει τη συνεργασία μεταξύ των παρόχων, όπως επίσης και τη διαφάνεια. Από την άλλη πλευρά, είναι δύσκολη η εφαρμογή της απαραίτητης διακυβέρνησης και ελέγχου χωρίς να επιδεινωθεί η γραφειοκρατία και η αναποτελεσματικότητα. Η επιδίωξη της αποτελεσματικότητας της αγοράς είναι ιδιαιτέρως αμφιλεγόμενη στην ψυχική υγεία, όπου πολλοί επαγγελματίες κρατούν αμυντική στάση σε σχέση με τους κινδύνους που ελλοχεύουν για τους ευάλωτους ασθενείς και τις παραδοσιακές μορφές επαγγελματικής εργασίας. Οι εξελίξεις και οι συζητήσεις που λαμβάνουν χώρα στο Ηνωμένο Βασίλειο ενδέχεται να είναι διδακτικές και αλλού. Κλείνουμε το άρθρο με μια σειρά ερωτήσεων που μπορεί να τροφοδοτήσουν τη περαιτέρω συζήτηση και την αξιολόγηση των υπηρεσιών ψυχικής υγείας διεθνώς.

Λέξεις ευρετηρίου: Υπηρεσίες ψυχικής υγείας, ανάθεση υπηρεσιών, παροχή υπηρεσιών, Ηνωμένο Βασίλειο (UK).

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Special article
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NICE recommendations for psychotherapy in depression: Of limited clinical utility

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In 2009/10 NICE partially updated its guidelines on the treatment and management of depression in adults. Due to methodological shortcomings the recommendations for psychotherapy must be treated with caution. Despite recognising the heterogeneous and comorbid nature of depression, and the limitations of depression as a unitary diagnostic category, NICE treats depression as if it were a unitary entity differentiated only by severity. The guidance ignores important aetiological factors such as trauma, loss and maltreatment, personality and interpersonal difficulties. It excludes the largest naturalistic studies on clinical populations treated in the National Health Service on the grounds that they are observational studies conducted in heterogeneous groups with mixed neurotic disorders. It unquestioningly accepts that the "brand" of psychotherapy has construct validity, and ignores psychotherapy process research indicating significant commonalities, and overlap, between treatment modalities and evidence that individual practitioner effects are larger than the differences between treatment modalities. It fails to consider patient differences and preferences, which are known to influence uptake, completion and response. It takes an exclusively short-term perspective on a chronic relapsing disorder. It does not consider the evidence for longer-term treatments. It is of special concern that NICE misrepresents the findings of its own systematic review by implying that CBT and IPT are superior treatments. NICE's systematic review actually found no evidence of superiority between CBT, IPT, psychodynamic psychotherapy, or counselling. Based on the exclusion of much clinically relevant research demonstrating the effectiveness of psychodynamic psychotherapy and counselling many commentators have alleged a bias towards CBT in the guidance. With regard to service delivery NICE proposes the replacement of psychiatric assessment and individualised treatment plans, with an unproven stepped-care model. These clinical and theoretical limitations, perceived bias in the selection of studies, neglect of patient differences, preferences and values, misrepresentation of results of the systematic review, and the

proposal for an unproven service delivery model together seriously undermine the validity of the guidance. The guidance, lacking validity is of questionable use, it undermines patient autonomy, professional expertise and, ultimately, patient welfare.

Key words: Depression, psychotherapy, guidelines, NICE.

The National Institute for Health and Clinical Excellence (NICE) provides national guidance on promoting good health and preventing and treating ill health. It aspires to be based on the best available evidence and involve all stakeholders in a transparent and collaborative manner.[1] Once published, health professionals (and employing organisations) are expected to take NICE guidance fully into account when deciding treatments.[2] The guidance on depression is aimed at clinicians, managers and commissioners. It makes recommendations on assessment, pharmacotherapy, psychosocial interventions, relapse prevention and service delivery.

The full updated guideline on depression (707 pages)[3] starts by describing depression as a broad, heterogeneous condition, influenced by diverse biological, psychological and social factors, and concludes that current diagnostic systems do not capture this complexity. However, having established these facts the guideline oversimplifies in key areas. Firstly it treats depression as a unitary diagnosis. Secondly it takes different psychotherapies at face value as representing distinct well-characterised interventions rather than the complex interventions that they are. Thirdly it treats patients as homogenous, without comorbidity, personality traits or preferences that moderate their responses to treatment. Fourthly it only considers short-term studies in what is a chronic relapsing disorder. Fifthly it excludes effectiveness studies, because of diagnostic heterogeneity or not being from randomised controlled trials (RCTs). In addition to these oversimplifications NICE actually misrepresents the results of its systematic review and erroneously implies that it has demonstrated that cognitive behavioural therapy (CBT) and interpersonal therapy (IPT) are superior treatments, whereas it has actually showed a lack of difference. Finally NICE recommends replacing clinical assessment and personalised treatment with an untested service delivery model.

Clinicians will be only too aware that "pure depression" if it exists at all rarely comes to the attention of psychiatrists working in the National Health Service, where comorbidity of all kinds and clinical heterogeneity are the norm. Epidemiological data suggest that NICE's model of depression separate from mixed neurotic conditions does not exist, the depressive syndrome overlaps with other common neurotic conditions.[4] Depressive symptoms occur in most mental and many physical disorders. Just consider the core depressive syndromes; depressive adjustment reactions, dysthymia and melancholia:[5] Adjustment disorder may be criticized for vagueness and medicalising problems of living.[6] Dysthymia is defined by mild symptoms, but sufferers spend more time depressed, have more admissions, more self-harm,[7] higher rates of personality disorder,[8] and it is more resistant to brief psychotherapy.[9] Depressive episodes have worse prognoses when co-occurring with dysthymia.[10] Furthermore depression has diverse aetiologies: Depressions arising from feelings of loss and activation of the attachment system (anaclitic depression) are associated with tearfulness, somatic complaints, parasuicide and care seeking. Depressions associated with failure, and activation of the social rank system (introjective depression) lead to fatigue, pessimism, guilt, inability to seek help and serious suicide attempts.[11,12] Anaclitic and introjective depressions appear to have differential responses to psychotherapy.[13] Some depressive behaviour can be seen as adaptive:[14] After loss of an attachment figure, depression inhibits searching and pro-

test when it has become futile. In respect of social dominance and competition the depressive state may operate as an unconscious, involuntary, losing strategy, enabling the individual to accept defeat and accommodate to what would otherwise be unacceptably low rank.[15] Displays of unhappiness also evoke sympathy and caring from others.[16] Understanding the functions of depression helps distinguish between situations in which depression may be considered in some way adaptive, and where it is dysfunctional.[17] Most patients with clinically significant depression meet the criteria for several different diagnoses and personality dysfunctions.[18] Co-morbidity is critically important in outcome research.[19] Depression arising in the context of early relational trauma (childhood bereavement, abuse or neglect) changes brain function[20] and may be differentially responsive to psychotherapy rather than pharmacotherapy.[21] The patients referred to secondary care psychotherapy services with depressive symptoms have high levels of personality disorder, psychotic disorders, comorbid neurotic disorders, and psychosocial or behavioural difficulties.[22]

As NICE itself writes in its guidance on the treatment of depression in children:[23] "the most significant limitation (to the evidence base) is the concept of depression itself... it is too broad and heterogeneous a category, and has limited validity as a basis for effective treatment plans. A focus on symptoms alone is not sufficient because a wide range of biological, psychological and social factors have a significant impact on response to treatment and are not captured by the current diagnostic systems" (p9).

Is the "brand" of psychotherapy the most useful level of analysis? In the guideline the different 'brands' of psychotherapy are accepted at face value as having construct validity. However the literature on psychotherapy process research reveals that psychotherapy is a complex intervention, and that 'brand' of psychotherapy has a loose relationship to what takes place within psychotherapy or what the effective ingredients of successful psychotherapy are. Psychotherapies are often considered to have non-specific effects (qualities inherent in any helping relationship that improve morale or lead to personal development) and specific effects (well defined intentional actions by the psychotherapist, usually considered as techniques). Both types of effects have been shown to be important.[24] The branding of different modalities of psychotherapy belies fundamental overlap in psychotherapeutic processes, for instance in the US National Institute of Mental Health's 1985 Treatment of Depression Collaborative Research Program (TDCRP) IPT was found to correlate more strongly with the CBT prototype than the IPT prototype.[25] Psychoanalytic psychotherapy often contains significant CBT elements, and change-promoting processes in CBT can be psychoanalytic.[26] Convergence is greater when conducted by master therapists.[27] Rigid adherence to a particular model can be negatively associated with outcome,[28,29] and effective therapists adjust their use of techniques to the individual patient.[30] This has lead to calls for a move away from what 'brand' is best, to what techniques or interpersonal processes achieve what ends with which kinds of patients.[31] If specific techniques account for little of the variance in outcome, then what are the change promoting ingredients? In psychotherapy, as in psychiatry generally, the interpersonal relationship is often said to be the basic vehicle for producing improvement. The TDCRP showed that the contribution of the therapeutic alliance outweighs the modality of treatment, whether CBT, IPT, imipramine or placebo.[32] Even with pharmacotherapy individual psychiatrist effects accounted for more variance in outcome than did medication over placebo (9.1% *vs* 3.4% of variance in BDI score).[33]

The third oversimplification is ignoring individual differences and preferences, instead treating patients as homogeneous and passive recipients of psychotherapy. Outcome in psychotherapy and psychiatry is generally highly personal and can be difficult to measure precisely. Increasing emphasis is placed on patient values and recovery. Patient preferences strongly influence take-up and completion rates in mental health treatments.[34] The

personality characteristic perfectionism predicts poorer response to brief treatments.[35] Different personality types respond differentially to exploratory versus supportive treatments, and to short-term versus long-term treatments.[36] Personality dysfunction reduces treatment responses in depression.[37] Patients with borderline personality traits may even be harmed by short-term or directive treatments.[38,39] Interestingly the full guideline contains seven personal accounts of depression (p. 52–68), the majority identified long-term psychodynamic psychotherapy and counselling as most helpful, none preferred CBT. Most wrote about the importance of making sense of childhood trauma and difficulties.

Unfortunately short-term psychological and pharmacological treatments are only partially effective in the treatment of depression, at 1-year follow-up about 60% of those treated with drugs still meet criteria for caseness,[40] and despite improving depression they do not lead to normal mood.[41] Despite these limitations of short-term treatments NICE excluded evidence for differential outcomes in long-term psychotherapy because the research is in mixed neurotic conditions or is observational.[42,43]

The exclusion of much research supporting psychodynamic psychotherapy and counselling on the grounds that it was conducted in heterogeneous groups with mixed neurotic disorders[44] or was from observational studies,[45] of long-term psychodynamic psychotherapy, both RCT[42–46] and observational,[43–47] and of cost effectiveness,[48,49] lead many commentators to the consultation phase to suggest a bias towards CBT.[50] Close reading of the draft guideline[51] reveals that the decision to withdraw the previous recommendation for psychodynamic psychotherapy "was influenced by contextual changes in the NHS including the significant increase in evidenced based psychological interventions (guided self help and CBT) made available through the IAPT programme" (p. 196). This commitment to one model, self-help and CBT, introduces bias and undermines the impartiality and credibility of the guideline.

The exclusion of many well-conducted observational and naturalistic studies is unsatisfactory. RCTs have been described as "experimental tools used to test hypotheses not well designed to assess clinical effectiveness"[52] (p. 67). The danger of over reliance on RCTs with their controlled settings and atypical patients has been widely commented on.[53,54] There are specific problems in using RCTs to assess psychotherapy: Firstly, treatments cannot be blinded. Secondly, the act of randomisation may reduce the effectiveness of psychotherapy, because its effectiveness depends on the subjects active participation, beliefs and preferences.[55] Thirdly, while RCTs are excellent for assessing drugs, psychotherapy contains no directly acting chemical ingredient, and is analogous with a chemotherapy placebo.[56] RCTs are designed to control for –and exclude– precisely those interpersonal processes that are at the core of psychodynamic psychotherapy. Psychodynamic psychotherapy requires entering into an interactive, interpersonal process of exploration of the meaning of interpersonal events in the patients' life and in the psychotherapeutic relationship, and relationships cannot be randomised any more than friendship, values, or beliefs. Thus "the idea of evaluating the efficacy of psychotherapy by controlling for non-specific or placebo factors is based on a flawed analogy."[57] Fourthly RCTs are less reliable assessing complex interventions with multiple "active ingredients".[58] Naturalistic studies offer additional means of assessing the effectiveness of interventions, particularly complex interventions like psychotherapy.[59]

There is an irony that this NICE guideline, which only admits RCT evidence, has not been tested in any RCT or shown to lead to improved care.

Having systematically reviewed its selected evidence NICE identifies "no clinically important differences" between CBT, interpersonal psychotherapy (IPT), short-term psychodynamic psychotherapy and brief supportive counselling, behavioural activation or GP treatment as usual (Full Guidance[3] p. 234–235). Thus NICE's review actually supports the 'equivalence paradox' that different short-term

psychotherapies appear equally effective, globally, in the short-term, in a range of conditions. The equivalence paradox has survived over thirty years[60] and has been confirmed naturalistically in the NHS.[61] Even though the overall effectiveness is similar, this does not mean that all individuals or types of depression respond equally; individual factors significantly influence outcome. Despite the absence of evidence of superiority NICE recommends CBT and IPT alone. The full guidance states "cognitive behavioural therapies have the largest evidence base" (p. 291) and in the research recommendations section "CBT has the best evidence base for efficacy but it is not effective for everyone. The availability of alternatives drawing from a different theoretical model is therefore important" (p. 300). This essential detail is lacking from the shorter NICE Guidance[62] (64 pages) and Quick Reference Guide[63] (28 pages), which are most widely read, and are likely to be misconstrued as presenting evidence that CBT and IPT have been proven to be superior treatments.

With regard to service delivery NICE recommends the replacement of assessment by experienced clinicians able to refer on to a broad range of psychotherapeutic modalities according to clinical judgment and patient characteristics and preferences with a stepped-care model offering self-help, CBT and IPT. This is despite "very limited evidence from direct studies in the support of a stepped care model" (draft for consultation,[52] p. 100). This stepped care model creates an illusion of objective standards, but deprives patients of professional expertise, individualised treatment and choice.[64]

Depressions are characterised by the interplay of biological, social and psychological factors, shaped by the individual, education, social class, beliefs, values and environment. Judgement is required to separate abnormal from normal.[65] Idiographic patient factors and values are increasingly recognised in causation and recovery from depression.[66] Psychiatric treatment should be based on diagnosis and formulation after detailed clinical assessment, taking into account patient values and preferences.[67] Experienced clinicians consider a wide array of patient preferences, characteristics and values in deciding management.[68] A diagnosis of depression alone is insufficient for optimal clinical decision-making. The draft for consultation[52] states: "The guideline development group consider that it is important to acknowledge the uncertainly inherent in our current understanding of depression and its classification and that assuming a false categorical certainty is likely to be unhelpful and worst damaging" (p. 18). However the guidance does just that.

The needs of the majority of patients, who do not respond to CBT or relapse within two years (Full guidance p. 158), or for whom CBT is unacceptable or ill-suited, must be addressed. Can they benefit from other psychotherapeutic modalities? Do long-term treatments or different modalities have superior long-term outcomes? Which psychotherapeutic processes, cognitive, behavioural, affective or interpersonal, and which aspects of the patient, clinician, and clinician-patient relationship promote change? Which modalities or processes are best suited to whom?

In 2009 Andy Burnham, then Secretary of State for Health, speaking about the Improving Access to Psychological Therapies programme, declared: "IAPT stands and falls on choice" and henceforth will be "providing people with a choice between different NICE approved treatments, such as CBT, Interpersonal Therapy, Couples Therapy, Brief Dynamic Therapy, Counselling and Collaborative Care".[69] The recognition of the importance of choice and the shift from NICE's narrow recommendations for guided self help, CBT and IPT to a wider provision of "approved" therapeutic modalities is welcome. However the shift from "NICE recommended" to "NICE approved" begs the question of what process was followed by NICE in "approving" treatments, because this is not described in the guidance.

Within the narrow framework established by NICE the review and statistics may be technically correct, but the method chosen is inadequate to com-

prehend the complexity of clinical condition, the complexity of the interventions and the range of evidence available. This reduces the clinical utility of the guidance. Credibility is reduced by commitment to a particular model and "one-size-fits-all" ecological fallacy (assuming because certain interventions have general efficacy they should be applied routinely to all cases). The proposal to replace expert clinical assessment with an untested model is wrong and dangerous because by inappropriate restriction of choice it undermines patient autonomy, professional expertise and, ultimately, patient welfare.

Future revisions of the guideline should reflect what the data show, not simply "count votes"; use an ecologically valid definition of depression; pay due consideration to factors influencing outcome: heterogeneity, aetiology, comorbidity, patient preferences; and consider long-term psychotherapy and naturalistic trials of effectiveness. NICE should heed the advice of its own chair Michael Rawlins, who criticising the "undeserved pedestal" that RCTs occupy[70] quotes Bradford Hill, architect of the RCT:

Any belief that the controlled trial is the only way would mean not that the pendulum had swung too far but that it had come right off the hook.[71]

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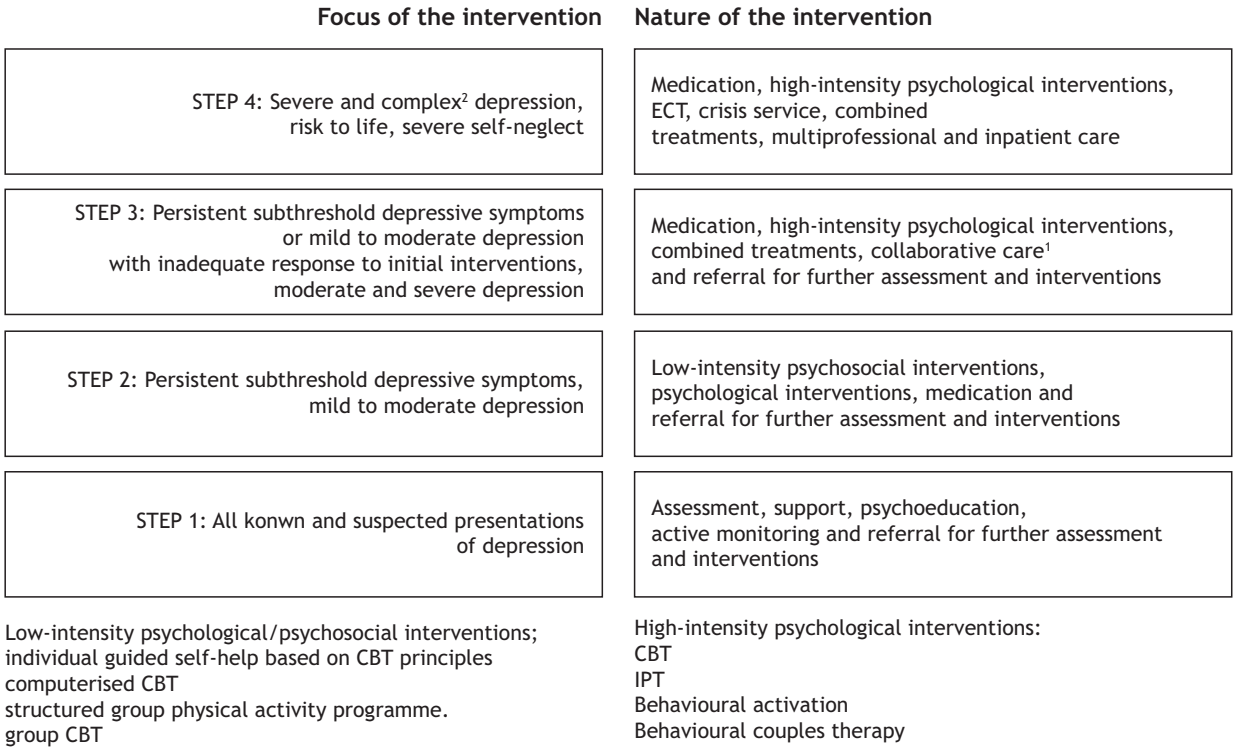

Συστάσεις από το NICE για την ψυχοθεραπεία της κατάθλιψης: Περιορισμένη κλινική χρησιμότητα

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Το 2009/10 το Εθνικό Ινστιτούτο Κλινικής Αριστείας (NICE) επικαιροποίησε εν μέρει τις κατευθυντήριες οδηγίες του για τη θεραπεία και τη διαχείριση της κατάθλιψης σε ενήλικες. Λόγω μεθοδολογικών αδυναμιών οι συστάσεις για την ψυχοθεραπεία θα πρέπει να αντιμετωπίζονται με προσοχή. Παρά την αναγνώριση της ετερογένειας και της συννοσηρής φύσης της κατάθλιψης, και τους περιορισμούς της κατάθλιψης ως ενιαίας διαγνωστικής κατηγορίας, το NICE αντιμετωπίζει την κατάθλιψη σαν να επρόκειτο για μια ενιαία οντότητα που διαφοροποιείται μόνον ως προς τη βαρύτητα. Οι οδηγίες αγνοούν σημαντικούς αιτιολογικούς παράγοντες, όπως το ψυχολογικό τραύμα, η απώλεια και η κακομεταχείριση, η προσωπικότητα και οι δυσκολίες στις διαπροσωπικές σχέσεις. Αποκλείει τις μεγαλύτερες νατουραλιστικές μελέτες σε κλινικούς πληθυσμούς μέσα στο Εθνικό Σύστημα Υγείας (NHS) με την επιχειρηματολογία ότι είναι μελέτες παρατήρησης σε ετερογενείς ομάδες με μικτές νευρωτικές διαταραχές. Δέχεται αναντίρρητα ότι γενικότερα η ψυχοθεραπεία έχει δομική εγκυρότητα, και αγνοεί την έρευνα πάνω στη διαδικασία της ψυχοθεραπείας που δείχνει σημαντικές ομοιότητες και επικαλύψεις μεταξύ των διαφόρων ειδών ψυχοθεραπείας, και στοιχεία που δείχνουν ότι η επίδραση του θεραπευτή είναι σημαντικότερη από τις διαφορές μεταξύ των ειδών ψυχοθεραπείας. Αποτυγχάνει να εξετάσει τις διαφορές και τις προτιμήσεις των ασθενών, οι οποίες είναι γνωστό ότι επηρεάζουν την άποψη για την ψυχοθεραπεία, την ολοκλήρωση και την ανταπόκριση στη θεραπεία. Υιοθετεί μια αποκλειστικά βραχυπρόθεσμη προοπτική για μια χρόνια υποτροπιάζουσα διαταραχή. Δεν συμμερίζεται αποδεικτικά στοιχεία για τις μακροπρόθεσμες θεραπείες. Είναι ιδιαίτερα ανησυχητικό το γεγονός ότι το NICE διαστρεβλώνει τα αποτελέσματα των δικών του συστηματικών ανασκοπήσεων υπονοώντας ότι η CBT και η IPT είναι ανώτερες ψυχοθεραπείες. Στην πραγματικότητα, συστηματική ανασκόπηση του NICE δεν απέδειξε ανώτερη καμία εκ των CBT, IPT, ψυχοδυναμική ή συμβουλευτική ψυχοθεραπεία. Με βάση την εξαίρεση κλινικά σχετικών ερευνών που αποδεικνύουν την αποτελεσματικότητα της ψυχοδυναμικής και της συμβουλευτικής ψυχοθεραπείας, πολλοί σχολιαστές έχουν ισχυριστεί ότι οι οδηγίες έχουν προκατάληψη υπέρ της CBT. Όσον αφορά στην παροχή υπηρεσιών, το NICE προτείνει την αντικατάσταση της ψυχιατρικής εκτίμησης και της εξατομικευμένης θεραπείας με ένα αναπόδεικτο μοντέλο κλιμακωτής φροντίδας. Αυτοί οι κλινικοί και θεωρητικοί περιορισμοί, η μεροληπτική επιλογή μελετών, η παράληψη στην αξιολόγηση των διαφορών, των προτιμήσεων και τις αξιών των ασθενών, η μη αντικειμενική παράθεση των αποτελεσμάτων των συστηματικών ανασκοπήσεων, και η πρόταση για ένα αναπόδεικτο μοντέλο παροχής υπηρεσιών, υπονομεύουν σοβαρά το κύρος των οδηγιών. Οι κατευθυντήριες οδηγίες με ελλιπή εγκυρότητα είναι αμφίβολης χρήσης, υπονομεύουν την αυτονομία του ασθενούς, την επαγγελματική εμπειρία και, εν τέλει, τη φροντίδα των ασθενών.

Λέξεις ευρετηρίου: Κατάθλιψη, ψυχοθεραπεία, κατευθυντήριες οδηγίες, NICE.

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Special article
Ειδικό άρθρο

Mental health and sexual activity according to ancient Greek physicians

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The ancient Greek physicians have not failed in their studies to indicate the beneficial role of sexual activity in human health. They acknowledged that sex helps to maintain mental balance. Very interesting is their observation that sex may help mental patients to recover. Nevertheless they stressed emphatically that sex is beneficial only when there is a measure in it, so they believed that sexual abstinence or excessive sexual activity affect negatively the mental and physical health of man. Ancient Greek physicians reached this conclusion by empirical observation. They tried to justify the mental imbalance, as the potential physical problems, which probably will be listed today in the psychosomatic manifestations, of people with long-term sexual abstinence or hyperactivity, based on the theory of humors which was the main methodological tool of ancient Greek medicine. Their fundamental idea was that the four humors of the body (blood, phlegm, yellow and black bile) should be in balance. Therefore they believed that the loss and the exchange of bodily fluids during sex help body's humors to maintain their equilibrium which in turn will form the basis for the physical and mental health. Although in ancient medical texts the irrationality presented by people in the aforementioned conditions was not attributed in any of the major mental illnesses recognized in antiquity, as mania, melancholy and phrenitis, our belief is that their behavior is more suited to the characteristics of melancholy, while according to modern medicine it should be classified in the depressive disorders. We have come to this conclusion, because common characteristics of people who either did not have sexual life or was overactive, was sadness, lack of interest and hope, as well as paranoid thinking that can reach up to suicide. Regarding the psychosomatic problems, which could occur in these people, they were determined by the ancient Greek physicians in the following; continuous headaches and heaviness, dilatancy, pain, dysuria and fever. But all these symptoms would disappear when the man gained a measure sexual activity, as was categorically stated by Galen. It is striking that these ideas were

maintained over time, starting already from the authors of the Hippocratic Corpus, from which the distinguished work De virginum morbis, refers indeed to women who reached the point of suicide due to the absence sexual life, hanging themselves or falling into wells and eventually passing to the works of Rufus of Ephesus, Soranus of Ephesus and Galen.

Key words: Sex life, depression, melancholy, mania, ancient greek medicine.

Introduction

It was a common notion amongst ancient Greek physicians that people must be sexually active[1] while maintaining a balance in this activity. This belief was based on the premise of the theory of humors on the foundations that either sexual abstinence or excessive sexual activity contributed to the unbalance of those humors in the body which results to disturbance of mental[2] and corporal health.[3] On the other hand a well-adjusted sexual life contributed to balanced humors and a good health. In fact ancient Greek physicians had observed that people with absent or excessive sexual life presented corporal and mental diseases,[4] mostly mania[5] (madness) and melancholy[6] (depression) and in order to explain the pathophysiology of these diseases they used the theory of the four humors, which was their basic methodological tool.[7]

The Hippocratic corpus

From the Hippocratic Corpus[8] we are informed that one of the oldest prognoses according to Hippocratic school of medicine is that not only athletes but also those who suffered from diseases, knew that their health will deteriorate in case of lack of food, of over-eating and over-drinking, of not walking or of excessive sexual activity as it is described in the book *Prorrheticon* (Hippocrates Med. et Corp. *Prorrheticon* 2.1.14–19).[9] Moreover, in the book *De morbis popularibus* it is highlighted that it should be a measure in sexual life as in hunger, in food, in drinking, in sleeping, in physical exercise and in fatigue, in order to maintain a healthy body (Hippocrates Med. et Corp. *De morbis popularibus* 6.6.2.–3).[10] However it is stressed that sexual activity is an element of health (Hippocrates Med. et Corp. *De morbis popularibus* 6.8.23.1–2).[10]

A very important work on sexual life in Hippocratic Corpus can be found in the book about the diseases of the virgins, *De virginum morbis* (Hippocrates Med. et Corp. *De virginum morbis* 1.1–45),[11] not only because there the theory of humors is applied in the analysis of the sexual life, but also because it is a work that clearly deals with mental and psychosomatic problems that derive from sexual deprivation.

This work indicates that sexual intercourse helps the body to maintain the equilibrium of the humors by loosing and receiving liquids. Furthermore the absurdity of a woman without a sex life is emphasized, which leads sometimes to committing suicide, that is why there is the advice of a sooner than later beginning of sexual life. In this situation the cause of the insanity is attributed to the theory of humors and especially in a specific state which is formed in the blood. It is believed that blood is accumulated in the area of the diaphragm (locus of logic)[12] and the heart and thus –according to its characteristics– it causes a special paranoiac manifestation that is respectively the same as that of the main mental diseases in antiquity, mania,[5] melancholy,[13] phrenitis.[14] The paranoia of the virgins could be milder or more severe. When it was milder, it was believed that the accumulated blood was transformed to phlegm[8] provoking acute inflammation, and when it was severe this blood was septic. In these severe cases women could commit suicide, either by falling into a well or hanging themselves, while on the milder cases they presented depressive manifestations.

As much as the physical problems are concerned there is fever that comes and goes, as well as weakness in mobility for women, which is attributed to the accumulation of blood to the extremities. It is considered a consequence with the least problems as it is not life threatening. We would say that these are part of the psychosomatic manifestations, since

psychological distress can cause fever, that comes and goes as it is already mentioned in the text, and immobility which is characteristic of malaise and the lack of energy as a sign of weakness which are seen in the people with mental disorder.

Finally, the direct advice of an early beginning of a sexual life and childbearing is an empirical observation of ancient physicians pointed also by the writer of this work, which nonetheless conforms with the contemporary approach of the topic as well as with the contemporary conception that sexual activity can stimulate and help a person with mental problems.

Views of other physicians in ancient Greece

Rufus of Ephesus (1st century AD) would be one to embrace moderation in sexual life as we learn from the Byzantine physician, Aetius of Amida (1st half 6th century AD). The physician believes that intercourse is a natural activity and thus anything that is natural is not harmful. On the contrary it becomes harmful when moderation is lost and sexual activity is constant and at disagreeable time. He will therefore stress that this constant activity must be avoided when there is a disease in the nerves (paralysis and other neurological diseases related with movement), in the thorax, in the kidneys, in the waist and when there is ischialgia or podalgia. We would point out the reference to the thorax illness which gives the impression of pointing to a respiratory or heart problem which can be aggravated by intercourse (Aetius Med. *Iatricorum liber iii* 8.1–6).[15]

Similar ideas we find in the work of another Byzantine physician, Oribasios of Pergamon (325–395/6 AD), who also preserves the ideas of Rufus of Ephesus. In the text of the Byzantine physician we are informed that the ancient Greek physician does not praise cravings but suggests more restraint, especially if there is disease in the bladder, in the kidneys or epilepsy or mania which defers from the work of Aetius of Amida. In addition to the various physical diseases the observation introduced here is that in a manic patient sexual activity may deteriorate the condition. However another interesting suggestion is that when urges are under control and are acted upon in moderation then the body can cope with future diseases. Lastly, the general rule is emphasized that man must combine the desires of the soul in harmony with those of the body, when it allows it, while excessive desire only serves the body; pointing clearly that people must not be prays to their physical desires of sex (Oribasius Med. *Collectiones medicae* 6.38.25.4–6.38.26.3).[16]

In another part of the work of Oribasios of Pergamon are preserved the suggestions of Rufus of Ephesus for what should be done in order to regain physical and mental balance in the case of a man being harmed by excessive sexual activity. He should therefore take a small number of walks, to take warm baths, have fresh food that will empower him, receive plenty of fluids, and sleep well enough and not to be agitated from rage, sadness, excessive entertainment, fever, perspiration, vomiting, drunkenness, fatigue, too much heat and too much cold (Oribasius Med. *Collectiones medicae* 25.1.1–25.1.8).[16]

Oribasios of Pergamon also saved Rufus' of Ephesus ideas about the benefit a person gets from sexual activity, which are based on the eucrasy of humors of the body.[17] That is, it stresses that with sexual activity the body is emptied from the overgrowth of sperm and becomes more masculine. The positive influence touches also the soul because it resets the thought to accuracy and exempts from unrestrained anger. For this reason he points out that for the melancholic people sexual intercourse is a way of healing, while at the same time it makes mad people sane and is very useful to those who suffer from diseases related to phlegm. They eat more easily as they become anorexic. Also it is stressed that sexual intercourse helps many people to avoid frequent wet dreams (Oribasius Med. *Synopsis ad Eustathium filium* 1.6.1.1–1.6.4.1).[18]

Studying the views of Soranus of Ephesus (2nd half 1st century – early 2nd century AD) in his original work it is made very clear that he strictly follows the adaptation of the humoral theory concerning the topic of sexual life. He takes a closer look to the question of which is healthier for a woman, to stay virgin for a long period of time or to have sexual relations, quoting the various views of his predecessors.

The view in favor of the sexual relations is based on the arguments that not only sexually active women have sexual drives but also virgins. In fact some of these are considered to have experienced stronger

loving desires than the sexually active women. It is mentioned that some claimed that excretion of sperm was not harmful neither for women nor for men. Lack of norm harms the body when they constantly excoriate sperm. It is believed that they benefit when the excretion happens in regular bases so as to avoid clumsiness and discomfort, while many state that after the sexual activity they became more agile and braver (Soranus Med. *Gynaeciorum libri iv* 1.31.1.1–1.31.3.1).[19]

It is also made known that many women due to long widowhood presented urinal retention and a pain feeling when urinating but when they became sexually active again the problems ceased (Soranus Med. *Gynaeciorum libri iv* 1.31.3.11–1.31.4.1).[19] We can say that this observation clearly suggests psychosomatic problems due to lack of sexual life.

Soranus of Ephesus is opposed to the above mentioned idea, thinking that virginity for a long period is healthy because intercourse entails risks which he elaborated on his chapter *Hygiene*. He gives the example of animals which we see to be more robust than those that are prevented of having sexual interaction. Moreover he gives another example of women who keep their virginity by the law or because they are dedicated to their religion and Gods, who do not die easily from disease. He also explains that the difficulty in urine cleansing and body fat observed in virgin women is caused by not participating in the beneficial physical activities which drives them at the following discomforts. That is why he concludes that as much as in men as well as in women staying a virgin for a long period is healthy, which will benefit them in breeding (Soranus Med. *Gynaeciorum libri iv* 1.32.1.1–1.32.3.4).[19] We would say that the physician focuses more in the issue of prevention of infections related to sexual activity.

On the other hand studying the problem of fertility he finds that there must be erotic impulse and desire by men and women in order to be fertile; showing by this way their mood for intercourse as an element of health, following the established concept of Ancient Greek medicine (*Soranus Med. Gynaeciorum libri iv* 1.37.1.1–1.37.3.7).[19]

Galen (129 – ca. 210 AD) will follow the basic advice for moderation in sexual activity, commenting generally that just like any other activity the same applies for sexual activity, that correctness lies in a healthy quantity, quality and circumstances (Galenus Med. *Thrasybulus sive utrum medicinae sit an gymnasticae hygieine* 5.885.9–13).[20]

Galen discussed sexual issues in a special work called, *De venereis*, which was saved by Oribasius of Pergamon where once more exemplifies the application of the theory of humors in sexual life (Oribasius Med. *Collectiones medicae* 6.37.1.1–6.37.11.6.).[16]

In the beginning the wisely sexual function is pointed out as a healthy instruction. At that point the physician discusses the characteristics that the body must have during intercourse. Thus he emphasizes that even though none is healthy according to the Epicurus, more correct is the sexual activity with pauses, while during it the person should not feel uninhibited and think that he became lighter and with better breath. The time for intercourse is proper when the body is in the middle of all external conditions; neither overfull nor empty, neither cold nor overheated, or dried or really wet. If there must be some exaggeration, it should be minor. It is better for the body to be more heated rather than very cold and overfull, rather than empty and wet and overdried during sexual intercourse. Those who are weak due to lust become very ill. Those who are strong and have a disease related to phlegm cause a reduction to the rest humors. Harmless are the intercourses in wet and hot people and to those that by nature have a lot of semen. Lust also raises the temperature in robust. In those who are weaker the temperature rises and then falls greatly.

Furthermore he mentions the problems caused in body and soul during intercourse or in the absence of it, so we would say that he explores in detail the issues that had already been discussed by the physicians of the Hippocratic Corpus and Rufus of Ephesus. He stresses the facts that some of those who start intercourse at a young age end up patients. Some if do not have constant sexual intercourse feel heaviness in the head and develop fever, wish the worst and become spineless. Those of this nature, when being abstinent in sexual intercourse, end up stuporous and cumbersome, while some become unreasonably moody and hopeless like melancholic people, but all these stop at once with sexual intercourse; clearly referring to the work, *De virginum morbis*. Galen pon-

dering concludes according to the above that sperm retention is very harmful which is confirmed by his experience, hence he states that he met some people who for reasons of shame refrained from sexual activities, resulting to be stuporous and cumbersome.

Except of prompting for sexual activity, he does not forget to point out that those who are sickly due to age or other reasons but participate in sex life, should know that the reduce of strength is inevitable; reminding us the relevant views of Rufus of Ephesus.

Apart from this indirect source we must also stand in another reference in the work of this Byzantine physician who saves a relevant view of Galen. In this, he first discusses the beneficial properties of intercourse when treating mania or melancholia, a fact that shows how Rufus of Ephesus influenced Galen. It is also contained that sexual activity is beneficial in mania and melancholia, making a person more logical, while in a person in love it diminishes the excessive urge and passion, when the person has intercourse with a partner (Oribasius Med. *Collectiones medicae* 24.1.1–24.2.1).[16]

Conclusion

Sexual activity in ancient Greece was an act to preserve the balance between health and disease. Body and mind could have been afflicted in the case of absence or excess of intercourse. Since the era of Hippocrates and later on, in the works of a series of well-known physicians, sex was tightly connected to the theory of the four humours.

Ψυχική υγεία και σεξουαλική δραστηριότητα σύμφωνα με τους αρχαίους Έλληνες ιατρούς

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Οι αρχαίοι Έλληνες ιατροί δεν παρέλειψαν στις μελέτες τους να υποδείξουν τον ευεργετικό ρόλο της σεξουαλικής δραστηριότητας στην υγεία του ανθρώπου. Αναγνώρισαν ότι οι σεξουαλικές σχέσεις βοηθούν στη διατήρηση της ψυχικής ισορροπίας του ανθρώπου. Μάλιστα ενδιαφέρον έχει η παρατήρησή τους ότι η σεξουαλικές επαφές μπορεί να βοηθήσουν ψυχικά ασθενείς να αναρρώσουν. Όμως τόνιζαν εμφατικά ότι η σεξουαλική ζωή είναι ευεργετική μόνο όταν υπάρχει μέτρο σε αυτήν, γι' αυτό και υπογράμμιζαν ιδιαιτέρως ότι η σεξουαλική αποχή ή η υπερβολική σεξουαλική δραστηριότητα επιβαρύνουν αρνητικά την ψυχική, αλλά και τη σωματική υγεία του ανθρώπου. Στο συμπέρασμα αυτό κατέληξαν από την εμπειρική τους παρατήρηση. Προσπάθησαν να αιτιολογήσουν την ψυχική ανισορροπία, όπως και τα πιθανά σωματικά προβλήματα, τα οποία μάλλον σήμερα θα κατατάσσαμε στις ψυχοσωματικές εκδηλώσεις, των ανθρώπων με μακροχρόνια σεξουαλική αποχή ή υπερδραστηριότητα, με βάση τη θεωρία των χυμών που ήταν το κύριο μεθοδολογικό εργαλείο της αρχαίας ελληνικής ιατρικής. Έκριναν, δηλαδή, ότι η απώλεια και η ανταλλαγή σωματικών υγρών κατά τη σεξουαλική επαφή βοηθά στη διατήρηση της ισορροπίας των χυμών του σώματος, η οποία με τη σειρά της θα αποτελέσει τη βάση για τη σωματική και ψυχική υγεία. Αν και στα αρχαία ιατρικά κείμενα δεν αποδίδεται ο παραλογισμός που παρουσία-

ζαν οι άνθρωποι στις προαναφερθείσες συνθήκες σε κάποια από τις κύριες ψυχικές νόσους που αναγνωρίζονταν στην αρχαιότητα, δηλαδή μανία, μελαγχολία και φρενίτιδα, θα κρίναμε ότι η συμπεριφορά τους ταιριάζει περισσότερο στα χαρακτηριστικά της μελαγχολίας, ενώ σύμφωνα με τη σύγχρονη ιατρική αυτή θα πρέπει να κατατάσσεται στη νόσο της κατάθλιψης. Στο συμπέρασμα αυτό μπορούμε να οδηγηθούμε, γιατί κοινά γνωρίσματα των ανθρώπων που είτε δεν είχαν σεξουαλική ζωή ή ήταν υπερδραστήριοι, ήταν η αθυμία, η απουσία ενδιαφερόντων και ελπίδας, όπως και η παράλογη σκέψη που μπορεί να φτάσει μέχρι και την αυτοχειρία. Τα ψυχοσωματικά προβλήματα που ήταν δυνατό να εμφανιστούν σε αυτούς τους ανθρώπους, σύμφωνα με τους αρχαίους Έλληνες ιατρούς ήταν τα παρακάτω: συνεχείς πονοκεφάλοι, αίσθημα βάρους, δυσκινησία του σώματος, πόνος, δυσουρία, πυρετός. Όλα αυτά τα συμπτώματα όμως εξαφανίζονται όταν ο άνθρωπος αποκτήσει με μέτρο σεξουαλική δραστηριότητα, όπως υποστηρίζει ο Γαληνός. Είναι εντυπωσιακό ότι αυτές οι ιδέες διατηρήθηκαν διαχρονικά ξεκινώντας ήδη από τους συγγραφείς της Ιπποκρατικής Συλλογής, από την οποία θα ξεχωρίσουμε το έργο Περί Παρθενίων, στο οποίο μάλιστα γίνεται αναφορά σε γυναίκες που έφταναν ακόμη και σε αυτοκτονία, απαγχονιζόμενες ή πέφτοντας σε πηγάδια, εξαιτίας της απουσίας σεξουαλικής ζωής. Ανάλογες αναφορές γίνονται ακόμη στα έργα του Ρούφου του Εφεσίου, του Σωρανού του Εφεσίου και του Γαληνού.

Λέξεις ευρετηρίου: Σεξουαλική ζωή, κατάθλιψη, μελαγχολία, φρενίτιδα, αρχαία ελληνική ιατρική.

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Research article
Ερευνητική εργασία

Validity of the Greek Eating Disorder Examination Questionnaire 6.0 (EDE-Q-6.0) among Greek adolescents

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The aim of this study is to examine the validity of the Greek version of the Eating Disorder Examination Questionnaire 6.0 (EDE-Q-6.0) in a sample of adolescent pupils. EDE-Q is a self – report instrument that assesses attitudes and behaviors related to Eating Disorders (EDs). A two-stage identification protocol has been applied to the 16 schools that agreed to participate in the present study. Initially, 2058 adolescents, in class under the supervision of one research assistant and one teacher, completed a Questionnaire on socio-demographic data, the Greek EDE-Q-6.0 and the Greek Eating Attitudes Test (EAT-26) while their weight and height were measured. Six-hundred and twenty six participants, who had scores on EAT-26≥20 and/or were underweight or overweight, were considered as "possible-cases" while the remaining 1432 pupils of the sample were thought as "non-possible cases". At the second stage, parents of 66 of the participants identified as possible-cases as well as parents of 72 participants from 358 controls randomly selected from the sample of "non-possible cases" agreed that their children would be examined by means of Best Estimate Diagnostic Procedure. Participants meeting DSM-IV-TR Eating Disorders criteria were identified. Receiver Operating Characteristics (ROC) analysis was applied to reveal EDE-Q's criterion validity. The kappa statistic test was used as measure of agreement between categorical variables at EDE-Q and at interview (the presence of objective binge eating episode, of self-induced vomiting, the use of laxatives and of excessive exercise). The Discriminant and Convergent validity were assessed using the non-parametric Mann-Whitney U test and by means of the Spearman's correlation coefficient, respectively. Nineteen cases of EDs were identified [one case of Anorexia Nervosa (AN), 13 cases of Eating Disorder Not Otherwise Specified (EDNOS), 5 cases of Binge Eating Disorder (BED)]. At the cut-

off point of 2.6125 on the EDE-Q's global scale the instrument screens with a sensitivity (Se) of 89.5% and a specificity (Sp) of 73.1%, a Positive Predictive Value (PPV) of 34.7% and a Negative Predictive Value (NPV) of 97.8% The same analyses for both sexes revealed a cut-off point of 2.612 for females and of 3.125 for males on the global EDE-Q-6.0 score (Se=84.62%, Sp=73.33% for females and Se= 83.33%, Sp= 84.09% for males), yielding a PPV and a NPV of 35.5% and of 96.5% for females and 41.7% and 97.4% for males, respectively. A very low agreement level, between EDE-Q and interview, was observed regarding the presence of objective bulimic episodes (OBEs) [k=0.191 (SE=0.057)] and the unhealthy weight control behaviors [k=0.295 (SE=0.073)]. Positive correlations were found between EAT-26 and EDE-Q-6.0 for both global scale and subscales (rho=0.50–0.57). The results suggest that EDE-Q-6.0, when using its global score, appears to be a proper screening tool for assessing the core psychopathology of eating disorders in community samples in two-stage screening studies since it distinguishes very well the cases from the non-cases. However, the assessment of the presence and frequency of pathological behaviours which characterize EDs appears to be problematic since adolescents, especially the younger ones, misunderstood terms like large amount of food and loss of control or misinterpret the motivation for excessive exercise. Therefore, marked discrepancies were observed between pathological behaviors self-reported at questionnaire and those detected at interview. We may assume that giving participants more information regarding the definition of these concepts may increase the accuracy with which the participants report these behaviors.

Key words: Eating disorders, Greek Eating Disorder Examination Questionnaire (EDE-Q), validity coefficients, adolescent pupils.

Introduction

According to the Academy for Eating Disorders position paper, eating disorders (EDs) are serious, biologically based mental disorders associated with the highest level of mortality and medical complications of any psychiatric condition, with impairment in emotional and cognitive function and significant worsening in quality of life.[1]

Early detection of EDs, in order to provide appropriate management, is critically important and as an alternative to the clinical interview, which is time-consuming, costly and needs specialized interviewers, two-stage EDs identification protocols have been developed. During the first stage, through screening instruments, individuals who are likely to have significant levels of eating pathology are identified, while, in the second stage, the clinical diagnostic interview is applied only to the proportion of people identified as possible cases during the screening.[2]

The Eating Disorder Examination Questionnaire (EDE-Q) is a self-reported, present-state version of the semi-structured clinical interview Eating Disorder Examination (EDE), and has the advantage to assess not only the eating disorder attitudes but also the specific ED behaviors and their frequency.[3] The psychometric properties of the EDE-Q have been examined in depth and, according to a recent review, the results revealed acceptable internal consistency and test-retest reliability.[4] In Greece, the use of the EDE-Q is limited; up to now there has been published a study regarding the reliability of the EDE-Q,[5] however there are no studies about its validity among adolescents.

The purpose of this study is to examine the validity of the Greek version of the EDE-Q-6.0 in a sample of adolescents (aged between 12–18 years) enrolled in secondary education.

Material and method

Overview

The study was carried out among secondary school adolescents (aged between 12–18 years) who live in northern Evros, a border prefecture of northeastern Greece. The study was reviewed and

approved by both the Pedagogical Institute of the Hellenic Ministry of Education and by the Ethics Committee of the General Hospital of Didymoticho, Greece. Participation involved informed consent from parents and pupils. From the 17 schools which were contacted, 16 agreed to participate in the study and for these schools a two-stage protocol was applied.

At the first stage, the students attending the school on the specific day of the study and who agreed to participate, in a single one-hour session in class, completed the study's questionnaires and had their weight and height measured. The study was presented as a research about the eating behaviors and body image concerns of adolescents. The pupils were informed that their participation was voluntary and they were assured of the confidentiality of their answers. Based on specific criteria pupils were classified as "possible" and "non-possible" cases.

During the second stage of the study, the parents of all possible cases and of a randomly selected sample of non-possible cases were contacted by phone and invited to visit the local Mental Health Center of Orestiada, together with their child, in order to be interviewed. They were kindly requested to bring with them any recent medical records of their child. Two reminder telephone calls were made in order to increase the participation rate.

Measures

During the first stage of the study the following questionnaires were administered:

a. An ad hoc questionnaire on socio-demographic data [age, gender (male-female), place of residence (rural-urban)].

b. The Greek version of EDE-Q-6.0: The current version (EDE-Q-6.0) is comprised of 28 items that focus on the past 28 days and allow assessment of both the core pathology of eating disorders (22 items) and the frequency of disordered eating behaviors (6 items). The 22 items generate four subscales scores (Restraint, Eating Concern, Shape Concern and Weight Concern) as well as a global scale score which is the average of the four subscales.[3] The frequency of the core ED behaviors is assessed in number of episodes occurring in the past four weeks. The Greek version was developed following World Health Organization (WHO) guidelines for translation and cross-cultural adaptation of self-reported measures in order to assure equivalency between the original source and the target version.[6] Both internal consistency and test-retest reliability of the Greek EDE-Q-6.0 were examined in a previous study which involved a sample of 257 adolescents, and both were found adequate (Cronbach's alpha coefficient for each of the EDE-Q subscales as well as for the global score ranged from 0.71 to 0.91, intraclass correlation coefficients and Pearson's correlation coefficients for each subscale and the global score of the questionnaire ranged from 0.55 to 0.70 and from 0.58 to 0.73, respectively while Kendal tau b coefficients indicating the test-retest reliability of items assessing behavioral features ranged from 0.22 to 0.57).[5,6]

c. The Greek version of the EAT-26: EAT-26 is a 26-item questionnaire designed to identify abnormal eating habits and concerns about weight and it is probably the most widely used standardized measure of symptoms and characteristics of ED.[7] A score exactly or above the cut-off score of 20 is considered to be an indicator of a possible eating disorder problem.[8] EAT-26 has been validated for Greek adolescents.[9]

d. Anthropometric measures. All participants had their weight and height measured in order to calculate the body mass index (BMI). The participants were classified as underweight, normal weight, overweight and obese by comparing their BMI with the BMI Percentile Charts of Greek Children and Adolescents[10] as follows: participants that had BMI less than that corresponding to the 3rd percentile for their age and sex on the above mentioned charts were considered as underweight. In addition, as proposed by the Obesity Task Force,[11] pupils were considered overweight or obese when their BMI exceeded the percentile curves that, at the age of 18 years, pass through the BMI of 25 kg/

m^2 and 30 kg/m^2 respectively. The remaining pupils were considered as normal weight.

The adolescents were identified as possible cases if they met at least one of the following three criteria: (a) they had EAT-26 scores of greater than or equal to 20, (b) they were underweight, or (c) they were obese. All other adolescents were considered as "non-possible" cases.

During the second stage of the study the parents of pupils identified as "possible cases" as well as parents of a randomly selected sample from pupils identified as "non-possible" cases were invited, to visit –together with their child– the Mental Health Centre of Orestiada. The pupils which constituted the control sample were selected according to the technique of systematic random sampling. Specifically, during the first stage of the study, when pupils delivered the questionnaires, a researcher wrote a code number on the first page of socio-demographic questionnaire. Two catalogs were developed from all these code numbers for "possible" and "non-possible cases", respectively. From the catalog of "non-possible cases" were selected, every fourth, the pupils who would become the control sample. The Best Estimate Diagnostic Procedure was used as the gold standard in order to identify the cases of EDs. This procedure, apart from the psychiatric interviews, employs all available sources of information (e.g. self-reported data from individuals and also information from family members and medical records) in order to reduce diagnostic errors and its use is particularly common in psychiatry because psychiatric illnesses –unlike their medical counterparts– have no external validators such as laboratory tests or radiological examinations.[12,13] Moreover, individuals with eating disorders, especially adolescents with AN, are less likely to admit the presence of pathology and have the tendency to minimize or deny the presence of symptoms since they may not recognize their eating behaviors as problematic and therefore their reports may not be accurate.[14] It is obvious that parents' reports are especially important as they are interested in eating patterns of their children and may be able to recognize disturbed eating behaviors. Generally, there are two forms of Best-Estimate Diagnostic Procedure. In the first one, two or more clinicians, independently, review the data and derive diagnoses, while in the second one a team of diagnosticians examine and discuss all data and by consensus arrive at best-estimate diagnoses.[15] In the present study we used the second procedure. Specifically, the interviews of participants and their parents were conducted by the first author, and subsequently a meeting took place, which involved another two psychiatrists. All accumulated data were discussed and diagnoses were determined by means of DSM-IV-TR criteria for EDs.

Statistical analysis

Descriptive analysis was done using mean ± Standard Deviation or median (Q1-Q3) for normally or non-normally distributed continuous variables and percentages for categorical variables. T-tests were used to check for differences between continuous normally distributed variables. Chi-square tests were used for the comparison of categorical variables.

Internal consistency of the EDE-Q, total and subscale scores, was tested by Cronbach's alpha coefficient.

To assess convergent validity scatter plots were created to examine first graphically the nature of association between EDE-Q-6.0 total and subscales and EAT-26 (linearity, outliers). After that, Spearman's correlation coefficient was chosen instead of Pearson's, to better describe the above relationships (a linear line could not always be assumed to describe the associations, and outliers were apparent in some cases).

The kappa statistic test was used as a measure of agreement between categorical variables at the EDE-Q-6.0 and at the interview with respect to objective binge-eating episode and unhealthy weight control behaviors. The ability of EDE-Q-6.0 then to discriminate between cases and non-cases (discriminant validity) was assessed using the non-parametric Mann-Whitney U test.

Receiver operating characteristics (ROC) analysis was conducted. Sensitivity, specificity, correct classification and likelihood ratios were calculated for all possible cut-off points of EDE-Q-6.0 global score both for the whole sample and for females and males separately. Finally, the EDE-Q-6.0 global scores which provide the optimal compromise between sensitivity and specificity were determined.

The PPV and NPV of the EDE-Q-6.0 as well as an area under the curve (AUC), at the optimal cut-off point, were also calculated. Results were considered statistically significant for $p<0.05$ ($\alpha=5\%$). All analyses were conducted using STATA 9.1.

Results

The sample

Overall, n=2058 pupils participated on the first stage of the study and provided data regarding their eating attitudes and behaviors as like as anthropometric data. From them n=626 and n=1,432 were classified as "possible" cases and "non-possible" cases, respectively. From the 626 participants' parents, who were classified as "possible" cases, only 66 (10.5%) agreed to be interviewed. From the 358 participants' parents, who were randomly selected as controls from the sample of 1432 pupils who were classified as "non-possible" cases, only 72 (20.1%) agreed to be interviewed. So, one hundred and thirty-eight adolescents and their parents took part in the second part of the study.

A description of the sample at the two stages is shown in table 1.

Out of the 2058 participants, 3.3% were classified as underweight, 61.2% as normal weight, 24.4% as overweight and 11% as obese. The EDE-Q-6.0 global score for females was 1.58 (SD=1.28) while for males it was 0.99 (SD=1.03). Regarding the 138 pupils examined at the second stage, 5.3% of them were underweight, 55.6% normal weight, 25.6% overweight and 13.5% obese. Females' EDE-Q-6.0 global score was 1.88 (SD=1.48) and males' 1.73 (SD=1.42).

Considering the second stage interviewed sample (n=138), there were no statistically significant differences between the pupils originally thought as possible cases (n=66) and non-possible ones (n=72), regarding age, sex and place of residence. However, interviewed possible cases compared to non-possible ones presented statistically significant higher BMI [(24.6±6.2) vs (22.2±3.2), t=2.84, p=0.005] and EDE-Q-6.0 global score [(2.65±1.35) vs (1.14±1.16), t=7.08, p<0.000].

Table 1. Description of the sample at the two stages.

		1st stage sample (n=2058)	2nd stage sample (n=138)
Demographics			
Age (mean±SD)		15.3±1.8	14.7±1.9
Sex (n%)	Male	1045 (50.8)	50 (36.2)
	Female	1013 (49.2)	88 (63.8)
Place of residence (n%)	Urban	1459 (70.9)	118 (85.5)
	Rural	599 (29.1)	20 (14.5)
BMI (mean±SD)			
EDE-Q (mean±SD)		23.1±4.5	23.3±5.0
Global scale			
Subscales			
	Restrain	1.28±1.20	1.83±1.46
	Eating concern	0.96±1.17	1.46±1.51
	Weight concern	1.58±1.52	2.17±1.69
	Shape concern	1.77±1.63	2.52±1.92

Internal consistency

Cronbach's alpha coefficients were 0.96 for EDE-Q global scale, 0.84, 0.80, 0.94 and 0.84 for the Restraint, Eating concern, Shape concern and Weight concern subscales respectively, indicating good internal consistency for all EDE-Q global scale and subscales.

Assessment of binge-eating behaviors

On the EDE-Q, 55 participants from the 138 interviewed, reported that they engaged in binge-eating behaviors. However, the interview revealed that only 9 actually presented objective bulimic episodes (OBEs) [k=0.191 (SE=0.057)]. Among these the number of OBEs on the EDE-Q and at the interview ranged from 1 to 28 and from 1 to 20, respectively.

Assessment of weight control behaviors

The use of weight control behaviors was reported by 46 participants on the EDE-Q but confirmed by only 11 (23.91%) participants at the interview [k=0.295 (SE=0.073)].

Sensitivity, specificity, positive and negative predictive value

At the second stage, using DSM-IV-TR diagnostic criteria, we detected 19 cases of EDs, 17 from those originally identified as possible cases and 2 from controls, 13 females and 6 males. One participant (female) met all DSM-IV-TR diagnostic criteria for Anorexia Nervosa (AN) restrictive type. The other 18 participants met the criteria for Eating Disorder not Otherwise Specified (EDNOS) among which five were clinical cases of Binge Eating Disorder (BED). Of the 13 cases diagnosed with EDNOS: 9 were sub-threshold clinical cases of AN restricting type (all criteria met except amenorrhea while body weight was over and below the 85% of EBW in 8 and 1 participants, respectively), 2 were sub-threshold clinical cases of AN binge eating/purging type (all criteria met except amenorrhea and body weight over the 85% of EBW) and 2 were sub-threshold clinical cases for BN purging type (all criteria met but frequency of binge eating and compensative behaviors were lower than required).

The mean age of the cases group was 15.2 years (SD=1.8) while that of non-cases was 14.5 years (SD=1.9) (t=1.93, p=0.056). The mean BMI was 25.84 for the cases group and 21.70 for the non-cases (t=5.75, p<0.001). From the 19 cases, six (31.5%) were classified as obese (four males and two females) and one (female) as overweight.

Tables 2 and 3 provide an overview of sensitivity, specificity, correct classification and likelihood ratios at the various cut-offs of EDE-Q-6.0 for the whole sample of 138 cases and as well as for females and males separately. The optimal compromise between sensitivity and specificity was achieved at a score of 2.6125 (Se=89.47%,

Table 2. Sensitivity, specificity, correct classification and Likelihood ratios for EDE-Q various cut-off points (n=138).

Cut-off point	Sensitivity	Specificity	Corrected classification	LR^+	LR^-
2.4	100	70.59	74.6	34.0	0.0
2.6125	89.47	73.11	75.3	33.2	0.14
2.85	84.21	77.31	78.2	37.1	0.20
3.125	73.68	81.51	80.4	39.8	0.32
3.281	73.68	81.51	80.4	39.8	0.32
3.85	42.11	91.60	84.7	50.1	0.63
4.168	36.84	97.48	89.1	146.1	0.64
4.262	26.32	99.16	89.1	313.1	0.74

LR^+=Positive likelihood ratio, LR^-=Negative Likelihood ratio

Table 3. Sensitivity, Specificity, correct classification and Likelihood ratios for EDE-Q various cut-off points for females (n=88) and males (n=50).

Cut-off point	Sensitivity	Specificity	Corrected classification	LR^+	LR^-
Females					
2.4	100.00	72.00	76.14	35.7	0.00
2.612	84.62	73.33	75.00	31.7	0.20
2.875	76.92	76.00	76.14	32.0	0.30
3.137	69.23	81.33	79.55	37.0	0.37
3.5	46.15	86.67	80.68	34.6	0.6
4.243	30.77	97.33	87.50	115.3	0.7
Males					
2.493	100.00	68.18	72.00	31.4	0.00
2.85	100.00	79.55	82.00	48.8	0.00
3.125	83.33	84.09	84.00	52.3	0.19
3.512	50.00	90.91	86.00	55.0	0.55
4.062	33.33	95.45	88.00	73.3	0.69
4.262	16.67	100.00	90.00		0.83

LR^+=Positive likelihood ratio, LR^-=Negative Likelihood ratio

Sp=73.11%) yielding a PPV of 34.7%, a NPV of 97.8% and a likelihood ratio for a positive test of 33.2. In addition, ROC analysis demonstrated an AUC of 0.88% (CI={0.82, 0.94}) which, according to Swets, indicates moderate accuracy.[16]

The same analyses for both sexes revealed a cut-off point of 2,612 for females and of 3,125 for males on the global EDE-Q-6.0 score (Se=84.62%, Sp=73.33% for females and Se=83.33%, Sp=84.09% for males), yielding a PPV and a NPV of 35.5% and of 96.5% for females and 41.7% and 97.4% for males as well as a likelihood ratio for positive test of 31.7 and of 52.3 for females and males, respectively.

Discriminative validity

Scores on the EAT-26 and the EDE-Q-6.0 global and subscales, for cases and non-cases are given in table 4. Individuals who were diagnosed as cases had significantly higher scores on both the EAT-26 and the EDE-Q-6.0 global and subscales' scores compared to non-cases.

Table 4. Values of the EDE-Q and the EAT-26 scales by eating disorder caseness.

	Cases (n=19)	Non-cases (n=119)	Mann-Whitney U z	p
EAT-26 (mean±SD)	25.5±8.5	13.0±7.3	6.75	<0.001
EDE-Q (Q1-Q3)				
Global scale	3.28 (3.1–4.26)	1.16 (0.39–3.11)	5.31	<0.001
Subscales				
Restrain	3 (2.4–4.4)	0.6 (0.2–2.2)	5.08	<0.001
Eating concern	2.6 (1.4–3.6)	0.4 (0–1.6)	4.68	<0.001
Weight concern	3.8 (3.4–4.6)	1.6 (0.4–3.4)	4.25	<0.001
Shape concern	4.6 (4.1–5.25)	1.63 (0.5–4)	5.02	<0.001

Convergent validity

Correlations between the EDE-Q-6.0 global and subscale scores with the EAT-26 for the sample of 138 pupils are presented in table 5. The results revealed moderate positive correlations from 0.50 to 0.57. The mean global score of the EDE-Q-6.0 for participants with EAT-26 score of less than 20 and greater than or equal to 20 was 0.95 (0.33–2.4) and 3.23 (2.4–4.14), respectively, and the difference was statistically significant (M-W U test z=5.62, p<0.001).

Discussion

The aim of the present study was to examine the criterion, convergent and discriminative validity of the EDE-Q-6.0 in a sample of Greek adolescents and to establish appropriate cut-off points for use in screening a general population sample. Many studies investigated the psychometric features of the EDE-Q and provided normative data for community samples[17] but, to our knowledge, until today, only two published studies indicated cut-off scores which optimize its sensitivity and specificity. These two studies involved women aged 18–45, were conducted by Mond et al and based on samples of 1,318 and 25 cases[19] respectively, they revealed cut-off scores of 2.3 [Se=0.83, Sp=0.96][18] and 2.80 [Se=0.80, Sp=0.8019 on the global scale of the EDE-Q.

The present study, based on the sample of 19 cases, revealed values of sensitivity and specificity for the EDE-Q-6.0, similar to those reported by Mond et al.[18,19] In this study we chose a cut-off point which optimizes sensitivity since screening tests – in opposition to diagnostic tests– aim to have high sensitivity in order to include all potential cases, especially if they are used to identify serious diseases that if missed could result in severe harm for the patient.[20] Anderson et al stated that the purpose of screening for the presence of eating disorder is not "necessary to determine an exact diagnosis... but rather to identify individuals who are likely to have significant levels of eating pathology and need further assessment".[2] Taking this into consideration a high sensitive instrument will be more suitable in screening for ED despite the high number of false positives which it yields.

The clinical cut-off score of 2,612 for females falls between the values of 2.3 and 2.8 reported by Mond et al[18,19] in the samples of adult women, whereas for males, as far as we know, the research is limited and until today only normative data regarding EDE-Q scores have been published. In the present study, for male adolescents, the cut-off score which had optimal sensitivity and specificity was higher than that for females, but this finding must be interpreted with caution on account of the small number of male participants and the preponderance of obese individuals, since values of the EDE-Q were found to increase significantly with BMI.[21] However, this high value is in concordance with that reported by Mond et al who found a higher cut-off point which optimized the validity coefficients for overweight participants than for normal weight ones (3.10 vs 1.98).[19]

Related to compensatory behaviors (self-induced vomiting, laxative misuse and excessive exercise) discrepancies were found between questionnaire and those reported at the clinical evaluation. Similar, Mond et al[22] found that about 42% of the participants who reported any self-induced vomiting or laxative misuse on the questionnaire denied these behaviors when they were questioned in a face-to-face interview. Concerning exercise in a compulsive way in order to lose weight or to prevent weight gain, it seems possible that this question on the questionnaire is misunderstood, and it

Table 5. Spearman correlations between EAT-26 & EDE-Q total scale and subscales (n=138).

EDE-Q & EAT-26 correlations	Spearman's rho
EDE-Q global scale	0.569
EDE-Q subscales	
Restraint	0.539
Eating concern	0.510
Shape concern	0.529
Weight concern	0.501

All correlations are significant at the 0.01 level (two tailed)

is mostly perceived that it refers to body building or to additional exercise for physical fitness and sports competition rather than as a compensatory behavior.

Similarly, a significant number of participants reported binge-eating behaviors but the presence of true OBEs was confirmed in only a few of them while the others, in fact, presented episodes of overeating, frequently, during parties, family celebrations, national or religious holidays. It was stated that assessment of self-reported binge-eating in youth is especially problematic due to ambiguity of terms such as "large amount of food" and "loss of control"[23] and that giving participants more information regarding the definition of binge-eating may increase the accuracy with which they report these behaviors on questionnaires like the EDE-Q.[24]

In the present study we identified only one case which completely fulfilled the strict diagnostic criteria of DSM-IV-TR for AN and 18 cases of EDNOS. These results are in concordance with those reported by two-stage epidemiologic studies which revealed that EDNOS is the most frequent diagnosis of EDs in adolescent samples.[25–30] The high frequency of EDNOS-AN which revealed in our study is similar to that reported by Muro-Sans and Amador-Campos who, in a sample of 1,155 adolescents, aged 11–17 years, found 12 cases of EDNOS-AN and 2 cases of EDNOS-BN.[31] However, we have to notice that no case of BN was diagnosed in the present study in opposite with some similar studies who reported, in addition to a significant number of EDNOS, some cases of BN as well.[28–30] Specifically, Pelaez-Fernandez et al in a group of 332 possible cases identified 28 cases of EDNOS, 3 cases of AN and 22 cases of BN.[28] Machado et al in a sample of 2028 female adolescents diagnosed 48 cases of EDNOS, 8 cases of AN and 6 cases of BN.[29] Similar, Vardar and Erzengin, interviewed 238 at risk participants from an initial sample of 2907 adolescents and found 44 cases of EDNOS, 1 case of AN and 23 cases of BN.[30] However, compared with aforementioned studies, participants in the present study recognized as having an ED, were younger (15.2+1.8 vs 16.19+1.33[29] and 17.01+0.86[30]). Pelaez-Fernandez et al do not report mean age of their cases but young adults were included in their sample, and it appears that 64.1% of the cases were over 16 years old.[28] It is well established, first, that the onset of BN, compared to that of AN, occurs at an older age with the majority of cases beginning during late adolescence and, second, the partial syndromes of BN are more prevalent among adolescents than among adults.[32] Younger age of our sample might be an explanation of not identifying any case meeting the strict diagnostic criteria for BN. Similar to our results, Isomma et al, in a sample of adolescents mean age 15.4 years, detected 2 cases of EDNOS-BN but no case of BN.[33] It is very possible the two cases of sub-threshold BN, which were diagnosed in the present study, represent early stages of a later full-blown syndrome. However, we have to notice that if we used the diagnostic criteria of DSM-V[34] which are wider, probably some cases of EDNOS would become full cases of AN or BN.

Moderate positive correlations were found between the EDE-Q-6.0 and the EAT-26 for both global and subscale scores. As far as we know only one study examined the convergent validity of the EDE- Q and the EAT-26 in an adolescent sample and found similar results (r=0.497).[35]

The results of the present study should be interpreted in the context of some limitations. A large number of participants were assessed and more than a quarter were considered as possible cases according to selection criteria, but unfortunately only a small proportion of them were interviewed. In similar studies the number of participants who did not participate in the interview was quite small in comparison to that of the present study (authors reported that they interviewed 69%,[29] 95%,[28] 96.6% 26 and 99.5%[30] of those identified as possible cases). One explanation may be that in these studies interviews were carried out at school, so both children and parents did not have any concern for this. On the contrary, in the present study we chose to interview children and parents at the local Mental health Center and perhaps this was why some of them were reluctant to participate in

the interviews. Another explanation may be that parents did not recognize their children's behaviors as problematic and consequently they did not have any reason for further investigation. Lectures to the Parents and Guardians Association in order to inform parents about the aims of the study as well as about the ED pathology did not increase the rate of participation. As in all studies which use self-reports the results can be affected by denial and social desirability, especially when the study, like the present one, involves individuals with eating disorders psychopathology which, deliberately may omit, conceal or distort their symptoms[36] or due to an impaired insight[37] or delusional body image beliefs,[38] may not be aware of their illness and may not admit that their behaviors are in fact symptoms of a mental disorder. Moreover, since the questionnaires were administrated in school class in the presence of a researcher and a teacher, the fear of revealing personal information to classmates and teachers might made some participants to minimize or hide their concerns and behaviors.

In addition, the small number of identified cases on which analysis of validity coefficients was based –although similar to those of Mond et al[18,19]– limits the generalization of results.

To our best knowledge, this is the first study which investigated the validity of the EDE-Q-6.0 in a sample of Greek adolescents and provided cut-off scores for both females and males. EDE-Q-6.0 was found to be moderately accurate in discriminating between individuals with eating disorders and those without, and it demonstrates good convergent validity. These results suggest that EDE-Q-6.0, when using its global score, appears to be a proper screening tool for assessing the core psychopathology of eating disorders in community samples in two-stage screening studies.

Εγκυρότητα της Ελληνικής εκδοχής του Eating Disorder Examination Questionnaire (EDE-Q-6.0) σε δείγμα Ελλήνων εφήβων μαθητών

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Σκοπός της μελέτης είναι η διερεύνηση της εγκυρότητας της ελληνικής εκδοχής του ερωτηματολογίου Eating Disorder Examination Questionnaire 6.0 (EDE-Q-6.0) σε δείγμα εφήβων μαθητών. Πρόκειται για ένα αυτοσυμπληρούμενο ερωτηματολόγιο με το οποίο αξιολογούνται στάσεις και συμπεριφορές που σχετίζονται με τις διαταραχές πρόσληψης τροφής. Αποτελείται από 28 ερωτήσεις. Βαθμολογούνται τόσο το συνολικό σκορ και οι 4 υποκλίμακες του ερωτηματολογίου (περιορισμός, ανησυχία για τη διατροφή, ανησυχία για το σχήμα του σώματος, ανησυχία για το βάρος του σώματος) όσο και η συχνότητα εμφάνισης επεισοδίων 6 τύπων διαταραγμένης συμπεριφοράς διατροφής [κατανάλωση ασυνήθιστα μεγάλης ποσότητας τροφής, αντισταθμιστικές συμπεριφορές (αυτοπροκαλούμενος εμετός, καταναγκαστική άσκηση, κατάχρηση καθαρτικών)]. Στα 16 σχολεία δευτεροβάθμιας εκπαίδευσης που δέχτηκαν να συμμετάσχουν στην παρούσα

έρευνα, εφαρμόστηκε ένα πρωτόκολλο δύο φάσεων. Αρχικά, 2.058 μαθητές, στη σχολική τάξη εντός μιας διδακτικής ώρας, παρουσία ενός μέλους της ερευνητικής ομάδας και ενός εκπαιδευτικού, συμπλήρωσαν ένα ερωτηματολόγιο δημογραφικών χαρακτηριστικών καθώς και τις ελληνικές εκδοχές του EDE-Q-6.0 και του EAT-26. Επιπροσθέτως, μετρήθηκε το βάρος και το ύψος τους. Βάσει συγκεκριμένων κριτηρίων οι μαθητές χαρακτηρίστηκαν ως «πιθανές» (n=626) και «μη-πιθανές» (n=1432) περιπτώσεις Διαταραχών Πρόσληψης Τροφής. Συγκεκριμένα, οι μαθητές θεωρήθηκαν «πιθανές» περιπτώσεις εάν παρουσίαζαν στο EAT-26 βαθμολογία ίση ή μεγαλύτερη του 20, εάν ήταν λιποβαρείς η εάν ήταν παχύσαρκοι. Στη δεύτερη φάση, οι γονείς των παιδιών που αναγνωρίστηκαν ως «πιθανές» περιπτώσεις καθώς και οι γονείς των παιδιών που, από το σύνολο των μαθητών που αναγνωρίστηκαν ως «μη-πιθανές» περιπτώσεις, επιλέχτηκαν ως ομάδα ελέγχου, προσκλήθηκαν να επισκεφθούν μαζί με τα παιδιά τους το Κέντρο Ψυχικής Υγείας Ορεστιάδας. Οι μαθητές που αποτέλεσαν την ομάδα ελέγχου επιλέχτηκαν με τη διαδικασία της συστηματικής τυχαίας δειγματοληψίας από το δείγμα των «μη-πιθανών» περιπτώσεων. Οι γονείς 66 μαθητών –από το σύνολο των 626 μαθητών– που χαρακτηρίστηκαν ως «πιθανές περιπτώσεις», καθώς και 72 μαθητών –από το σύνολο των 358 μαθητών– που επιλέχτηκαν ως ομάδα ελέγχου, δέχτηκαν να εξεταστούν τα παιδιά τους. Η διάγνωση τέθηκε χρησιμοποιώντας την Καλύτερη Δυνατή Διαγνωστική Εκτίμηση η οποία, εκτός από την ιατρική συνέντευξη περιλαμβάνει και όλες τις πηγές πληροφοριών (π.χ. πληροφορίες από τα μέλη της οικογένειας, από το οικογενειακό ιστορικό καθώς και από ιατρικές εξετάσεις) με σκοπό την ελαχιστοποίηση των διαγνωστικών λαθών. Εφαρμόστηκε η ανάλυση Receiver Operating Characteristics (ROC) για την εξέταση της Εγκυρότητας Κριτηρίου του EDE-Q-6.0. Η Διακρίνουσα Εγκυρότητα του EDE-Q-6.0 καθώς και η Συντρέχουσα Εγκυρότητα ανάμεσα στις βαθμολογίες του EDE-Q-6.0 και του EAT-26 αξιολογήθηκαν με το μη-παραμετρικό τεστ Mann-Whitney U αφενός, και αφετέρου με τον υπολογισμό του συντελεστή συσχέτισης Spearman. Ο συντελεστής Κάππα του Cohen χρησιμοποιήθηκε προκειμένου να αξιολογηθεί ο βαθμός συμφωνίας των κατηγορικών μεταβλητών στο EDE-Q-6.0 και στη συνέντευξη, σε ό,τι αφορά στην παρουσία των επεισοδίων υπερφαγίας και των αντισταθμιστικών συμπεριφορών. Βάσει των διαγνωστικών κριτηρίων του DSM-IV-TR διαγνώστηκαν 19 περιπτώσεις Διαταραχών Πρόσληψης Τροφής (ΔΠΤ) (μία περίπτωση Ψυχογενούς Ανορεξίας, 13 περιπτώσεις ΔΠΤ Μη Καθοριζόμενη Αλλιώς και 5 περιπτώσεις Διαταραχής Επεισοδιακής Υπερφαγίας). Στο διαγνωστικό όριο 2,6125 της συνολικής βαθμολογίας η ευαισθησία, η ειδικότητα, η θετική προγνωστική αξία και η αρνητική προγνωστική αξία του EDE-Q-6.0 ήταν 89,5%, 73,1%, 34,7% και 97,8%, αντίστοιχα. Η ανάλογη ανάλυση στα δύο φύλα υπέδειξε ως «διαγνωστικό όριο» το 2,612 (για τις θήλεις) (ευαισθησία=84,62%, ειδικότητα=73,3%, θετική προγνωστική αξία=35,5%, αρνητική προγνωστική αξία= 96,5%) και 3,125 (για τους άρρενες) (ευαισθησία=83,33%, ειδικότητα=84,09%, θετική προγνωστική αξία=41,7%, αρνητική προγνωστική αξία=97,4%). Ελάχιστος και μικρός βαθμός συμφωνίας παρατηρήθηκε σε ό,τι αφορά στην παρουσία των επεισοδίων υπερφαγίας [k=0,191 (SE=0,057)] και των αντισταθμιστικών συμπεριφορών [k=0,295 (SE=0,073)]. Τόσο η συνολική βαθμολογία όσο και οι βαθμολογίες στις υποκλίμακες του EDE-Q-6.0 βρέθηκαν να συσχετίζονται θετικά με τη βαθμολογία του EAT (Spearman's rho=0.50–0.57). Τα αποτελέσματα υποδεικνύουν ότι η ελληνική εκδοχή του ερωτηματολογίου EDE-Q -6.0, στη συνολική της βαθμολογία, φαίνεται να αποτελεί ένα έγκυρο εργαλείο για την αξιολόγηση της ψυχοπαθολογίας των ΔΠΤ στους έφηβους μαθητές. Ωστόσο, η αξιολόγηση της παρουσίας και της συχνότητας των διαταραγμένων διατροφικών συμπεριφορών, που χαρακτηρίζουν τις ΔΠΤ, φαίνεται να είναι προβληματική καθώς οι έφηβοι, κυρίως οι νεότεροι, παρανοούν όρους όπως ασυνήθιστα μεγάλη ποσότητα τροφής ή αίσθηση απώλειας ελέγχου και παρερμηνεύουν την έννοια της άσκησης με έναν καταναγκαστικό τρόπο. Ως εκ τούτου, παρατηρήθηκε μεγάλη ασυμφωνία ανάμεσα σε όσα δηλώθηκαν αυτο-αναφορικά και σε όσα διαπιστώθηκαν στη συνέντευξη. Πρόσθετες πληροφορίες που θα αποσαφηνίζουν αυτούς τους όρους είναι ενδεχόμενο να συμβάλουν σε μεγιστοποίηση της ακρίβειας με την οποία οι έφηβοι θα δηλώνουν, αυτο-αναφορικά, τις εν λόγω συμπεριφορές.

Λέξεις ευρετηρίου: Διαταραχές πρόσληψης τροφής, Greek Eating Disorder Examination-Questionnaire-6.0, εγκυρότητα, έφηβοι μαθητές.

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Brief communication article
Σύντομο άρθρο

Inter-rater reliability of the Greek version of CAARMS among two groups of mental health professionals

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There is increasing interest within the Greek psychiatric community in the early detection and prevention of psychotic disorders. To support this, there is a need for a valid and reliable tool to identify young people that may be at risk of developing a psychotic disorder. Our team has previously translated the Comprehensive Assessment of At-Risk Mental States (CAARMS). The validity of the CAARMS was ensured by the procedure of translation and the aim of the current study was to estimate the interrater reliability of the CAARMS Greek translation among residents in psychiatry and specialized mental health professionals. 43 mental health workers (27 residents in psychiatry and 16 specialized mental health professionals (i.e. 11 psychiatrists and 5 psychologist) participated in two seminars that covered theoretical information about the ultra high risk concept and training in the CAARMS. During the seminars, 10 vignettes with psychiatric history cases were presented, including healthy, ultra high risk and first episode psychosis. The mean correlated percentage of agreement with the correct answers regarding diagnosis of the presented history cases among all our subjects was 81.42, among specialized mental health professionals 77.88, and among residents 84.46. Intraclass correlation co-efficients were 0.994 for specialized mental health professionals and 0.997 for residents. The translated Greek version of CAARMS presents a satisfying interrater reliability when used by both residents and specialized mental health professionals. Residents declare even higher intraclass correlation co-efficients and mean correlated percentage of agreement than specialized mental health professionals, which indicate that residents are capable of using the CAARMS in early intervention units.

Key words: Early psychosis, prevention, CAARMS, Greek version, reliability.

Introduction

The Comprehensive Assessment of At-Risk Mental States (CAARMS)[1] has been designed by Yung et al. to assess psychopathology indicative of imminent risk of development of a first psychotic episode (FEP) and to determine if an individual meets the Ultra High Risk (UHR) criteria for developing a FEP. The original CAARMS has been tested regarding its inter-rater reliability and concurrent, discriminant and predictictive validity which have been found to be good to excellent.[1] The CAARMS has been translated and standardized into multiple languages, including Spanish, Swedish, Danish, German, French, Italian, Japanese, Chinese, Korean and Arabic.[2–5]

The growing interest of the Greek Psychiatric Community in the issues of early prevention in psychosis has been developing in recent years.[6] Some of the initiatives taken were the publication of a new book ("Early Psychotic Experiences. Signs, Symptoms and Interventions"),[7] the translation of the CAARMS[8] and the organization of presentations in daily meetings, training seminars and round tables in national and international congresses, regarding early prevention in psychosis issues. A "Hellenic Group for early intervention in Psychosis" was formed by specialists from many Greek University Psychiatric Clinics and organized scientific meetings. Representatives of Greek relatives' and patients' associations were invited and participated in one of those meetings. The translators of the CAARMS suggested (and got their suggestion published in an international journal) that the term sub-threshold prodromal state might be used instead of attenuated psychosis syndrome in DSM-V.[9] They have also presented in a congress preliminary findings regarding the translated CAARMS psychometric properties.[10]

The growing interest in issues of early prevention has led a number of mental health institutions in Greece, such as Eginition Hospital – 1st Department of Psychiatry, University of Athens, Attikon Hospital – 2nd Department of Psychiatry, University of Athens, the Mental Health Research Institute and the Psychiatric Clinics of the University of Thessaloniki, of the University of Ioannina and of the University of Patras, along with Hellenic Psychatric Association, to organize scientific presentations and collaborations, as well as training seminars, regarding early psychosis prevention programs. Since 2007, an early intervention service for psychosis has been operating in Ioannina, and has since been successfully established within the context of the local mental health network.[11]

In Athens University in particular, the 1st and 2nd Psychiatric Clinic, in Eginition Hospital and Attikon General Hospital respectively, took a few more steps in implementing such preventive strategies. Two new outpatient units have been installed in Eginition and Attikon Hospital regarding early psychosis.

The outpatient Eginition Hospital unit is addressed to young first degree relatives (15–45 years of age) of patients with psychosis, as well as probable ultra high risk patients referred by other psychiatric units of Eginition or other hospitals. Among them, those who are found to meet the Ultra High Risk criteria are selected and followed up. Appropriate psychological and pharmacological interventions (benzodiazepines and antidepressants or antipsychotic medication once they have transitioned to First Episode Psychosis) are implemented to them, if necessary. Those subjects are also studied regarding various psychosocial parameters, such as quality of life, personality traits, anhedonia, psychosis or schizophrenia proneness, as well as biological parameters.

It should be mentioned that investigators in those two hospitals had already experience in the research of first episode schizophrenia (FES) patients. From previous studies, various biological parameters were investigated as probable susceptibility risk factors for schizophrenia, such as the serum BDNF levels at the onset of schizophrenia and the BDNF Val66Met variant.[12] In other studies, it was demonstrated that activities released by P600 during working memory tasks may be involved in FES patients[13] and that second-pass

parsing process of information processing, as indexed by P600, elicited during a working memory test, is impaired in FES patients.[14] Methods demonstrating chromatin alterations of leucocytes of FES patients were studied as tools of early diagnosis, since decondensed chromatin is considered as a biological marker of schizophrenia.[15] So, it would be of great interest to search if such genetic, molecular, psychophysiological and other biological markers might be related to ultra high risk for psychosis patients. Our team in Eginition Hospital has also translated, back-translated in Greek and published another psychometric instrument used in early prevention, the SPI-A.[16]

Aim

The goal of this study was to estimate the reliability of the Greek translation of the CAARMS, regarding diagnosis of psychiatric history cases presented to our subjects and to compare two groups of mental health professionals regarding their inter-rater reliability for the positive subscales of the CAARMS. The Eginition early psychosis intervention outpatient unit trains residents in their last year of their training in psychiatry in the use of the CAARMS. Those residents participate in the estimation process of subjects referred to our unit. Thus, it is important for our unit to demonstrate that residents are equally capable as specialized mental health professionals in the use of the CAARMS, after being trained.

Material and method

The CAARMS was translated in Greek in collaboration with the authors of the original CAARMS. The validity of the CAARMS was ensured by the method of translation - back translation in Greek followed by the translators, according to the following directions proposed by the authors of the interview:

The original version of the CAARMS was translated into Greek by one person, then translated back by another separate person and then this back-translation was checked by an author of the original version of the CAARMS. Then, any discrepancies were resolved by discussion between the Greek translation team and an author of the English version of the CAARMS.

Our outpatient unit has organized two seminars, in which the participants were psychiatry residents and other mental health professionals who have completed their training in their specialty (i.e. 11 psychiatrists and 5 psychologists). In those seminars we gave them theoretical information about the ultra high risk concept, we presented the CAARMS and we gave them directions in which way they should rate subjects when using it. The translators of the CAARMS were the trainers in the two seminars. One of them, following the "train the trainer's model", was provided training in the use of the CAARMS by the CAARMS Training Coordinator of the time.

During those seminars, we presented to our subjects the same 10 vignettes with psychiatric history cases, which might belong to patients suffering from a first psychotic episode, to subjects in high risk for psychosis or to healthy ones. Those vignettes were provided by the authors of the CAARMS, in order to estimate reliability among mental health professionals using the CAARMS. Five of these vignettes were rated as part of the training, by discussing which might be the correct rating and final conclusion about diagnosis. Then, five vignettes were rated by our subjects in order to estimate their inter-rater reliability.

The two seminars were followed by 43 mental health professionals, 27 residents in psychiatry in the last year of education and 16 specialized mental health professionals (11 psychiatrists and 5 psychologists). Statistically, the SPSS, version 17, was used and the mean correlated percentage of agreement with the correct answers, regarding diagnosis and the severity and frequency of the three initial subscales of the CAARMS were estimated. The intraclass correlation coefficient was estimated separately in our two groups of specialized mental health professionals and of psychiatric residents.

Results

The mean correlated percentage of inter-rater agreement with the correct answers, regarding the categorization of the psychiatric history cases (Trait and State Risk Factors-TSRF, Attenuated Positive Symptoms – AIMS, Brief Limited Intermittent Psychotic Symptoms – BLIPS, normal, psychosis threshold) among our subjects, was 81.42%. The mean correlated percentage for residents was 84.46% and for specialized mental health professionals was 77.88% (table 1). The mean correlated percentage of agreement with the correct answers, regarding the severity and frequency of the three initial positive symptoms subscales is presented in table 2.

Two intraclass correlation co-efficients were estimated, one for the specialized mental health professionals and one for the residents. The intraclass correlation co-efficient for the specialized mental health professionals was 0.994, while for the residents it was 0.997.

Conclusion

The translated in Greek CAARMS is valid and reliable when used by mental health professionals in order to correctly diagnose psychiatric history cases. Both the group of specialized mental health professionals and of psychiatric residents exhibited high intraclass correlation co-efficients. Our findings show that psychiatric residents, even though they have not completed their training, were proven more reliable in using the CAARMS, after a short training in the use of that interview, than specialized mental health professionals. Thus, it seems that psychiatric residents after a short training are suitable for participating in prevention programs in which this interview is used.

The method used in order to estimate the inter-rater reliability of the translated CAARMS differed from the method used to estimate the inter-rater reliability of the original.[17] However, in both cases, the CAARMS exhibited satisfactory inter-rater reliability.

Greece, at the time being, is a country in economic crisis, so policy and economic issues should be taken into account, regarding the implementation of early prevention services. Specialists interested in shifting preventive interventions in psychosis from a model of secondary and tertiary prevention in psychosis to one of primary and secondary prevention have also to face negative attitudes towards early prevention, especially in such a difficult period for mental health services. Yet, there is a lack of financial programs assisting that effort of Athens in issues of early intervention. Thus, people interested in those services should have a deep interest in them and voluntarily elaborate time and energy in order to promote the establishment of those new preventive activities.

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Table 1. Mean correlated percentage of agreement with the correct diagnosis among all subjects, specialized mental health professionals and residents.

All subjects	81.42
Specialized mental health professionals	77.88
Residents	84.46

Table 2. Mean correlated percentage of agreement with the correct answers.

	Severity	Frequency
Unusual thought content	92.78	92.3
Non bizarre ideas	91.18	94.14
Perceptual abnormalities	97.56	97.02

Η αξιοπιστία μεταξύ εκτιμητών της Ελληνικής μετάφρασης της CAARMS σε δύο ομάδες επαγγελματιών ψυχικής υγείας

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Τα μέλη της Ελληνικής Ψυχιατρικής Κοινότητας επιδεικνύουν ένα αυξανόμενο ενδιαφέρον σχετικά με την πρώιμη ανίχνευση και πρόληψη των ψυχιατρικών διαταραχών, το οποίο έχει οδηγήσει έναν αριθμό δομών ψυχικής υγείας στην Ελλάδα στη διοργάνωση επιστημονικών παρουσιάσεων, συνεργασιών και εκπαιδευτικών σεμιναρίων σχετικών με προγράμματα πρώιμης παρέμβασης. Στο Πανεπιστήμιο των Αθηνών ειδικότερα, στην Ψυχιατρική Κλινική του Αιγινητείου Νοσοσκομείου λειτουργεί ένα νέο εξωτερικό ιατρείο πρώιμης παρέμβασης στην ψύχωση. Προκειμένου να αναγνωριστούν νέα άτομα ως υψηλού κινδύνου για ψυχωσική διαταραχή είναι απαραίτητο να μπορεί να χρησιμοποιηθεί ένα έγκυρο και αξιόπιστο εργαλείο μεταφρασμένο στα Ελληνικά. Η ομάδα μας πρόσφατα μετάφρασε την Comprehensive Assessment of At-Risk Mental States (CAARMS). Η εγκυρότητα της CAARMS διασφαλίστηκε μέσω της διαδικασίας που ακολουθήθηκε κατά τη μετάφρασή της. Ο στόχος της παρούσας μελέτης είναι η εκτίμηση της μεταξύ βαθμολογητών αξιοπιστίας της ελληνικής μετάφρασης της CAARMS σε δύο ομάδες, μία ειδικευομένων της Ψυχιατρικής και μία ειδικών επαγγελματιών της Ψυχικής Υγείας. Το ιατρείο πρώιμης παρέμβασης στην ψύχωση του Αιγινητείου Νοσοκομείου παρέχει εκπαίδευση σε ειδικευόμενους στο τελευταίο έτος της εκπαίδευσής τους στην Ψυχιατρική, στη χρήση της CAARMS. Οι ειδικευόμενοι αυτοί συμμετέχουν στη διαδικασία εκτίμησης των ατόμων που παραπέμπονται στο ιατρείο. Έτσι, είναι σημαντικό για το ιατρείο μας να διερευνηθεί εάν οι ειδικευόμενοι είναι εξίσου κατάλληλοι όσο οι ειδικευμένοι επαγγελματίες ψυχικής υγείας στη χρήση της CAARMS μετά από εκπαίδευση. 43 εργαζόμενοι στον χώρο της ψυχικής υγείας (27 ειδικευόμενοι στην Ψυχιατρική και 16 ειδικευμένοι επαγγελματίες ψυχικής υγείας) συμμετείχαν σε δύο σεμινάρια, τα οποία διοργανώθηκαν από το εξωτερικό ιατρείο πρώιμης παρέμβασης του Αιγινητείου. Στα σεμινάρια αυτά παρασχέθηκε θεωρητική ενημέρωση για το θέμα των εξαιρετικά υψηλού κινδύνου για ψύχωση καταστάσεων, έγινε παρουσίαση της CAARMS και δόθηκαν οδηγίες για τη βαθμολόγησή της. Οι μεταφραστές της CAARMS ήσαν οι εκπαιδευτές στα δύο σεμινάρια. Ένας από αυτούς, ακολουθώντας το «μοντέλο εκπαιδεύοντας τον εκπαιδευτή», εκπαιδεύτηκε στην CAARMS από τη Συντονίστρια στην Εκπαίδευση της CAARMS εκείνης της περιόδου. Κατά τη διάρκεια των σεμιναρίων παρουσιάστηκαν δέκα κείμενα περιπτώσεων ψυχιατρικών ιστορικών, που αφορούσαν είτε υγιείς είτε άτομα λίαν υψηλού κινδύνου για ψύχωση είτε με πρώτο ψυχωσικό επεισόδιο. Το mean correlated percentage of ageement με τις σωστές απαντήσεις αναφορικά με τη διάγνωση των παρουσιασθέντων ιστορικών μεταξύ του συνόλου των υποκειμένων της μελέτης ήταν 81,42, μεταξύ των ειδικών επαγγελματιών ψυχικής υγείας ήταν 77,88 και μεταξύ των ειδικευομένων ήταν 84,46. Τα intraclass correlation coefficients ήταν 0,994 για τους ειδικευμένους επαγγελματίες ψυχικής υγείας και 0,997 για τους ειδικευόμενους ψυχιάτρους. Η μεταφρασμένη ελληνική έκδοση της CAARMS παρουσιάζει μια ικανοποιητική μεταξύ βαθμολογητών αξιοπιστία όταν χρησιμοποιείται είτε από ειδικευόμενους ψυχιάτρους είτε από ειδικευμένους επαγγελματίες ψυχικής υγείας. Οι ειδικευόμενοι μάλιστα εμφανίζουν ακόμη μεγαλύτερα intraclass correlation co-efficients και mean correlated percentage of agreement από τους ειδικευμένους επαγγελματίες ψυχικής υγείας, γεγονός που σημαίνει ότι οι ειδικευόμενοι είναι κατάλληλοι να επιδίδουν την CAARMS σε μονάδες πρώιμης παρέμβασης.

Λέξεις ευρετηρίου: Πρώιμη ψύχωση, πρόληψη, CAARMS, Ελληνική μετάφραση, αξιοπιστία.

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Obituary
Νεκρολογία

Γεώργιος Στ. Καπρίνης

(1943–2015)

Στις 17 Ιουνίου 2015 έφυγε ξαφνικά για το μεγάλο ταξίδι στο επέκεινα ο Ομότιμος Καθηγητής του Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης Γιώργος Καπρίνης. Σύσσωμη η Πανεπιστημιακή Κοινότητα, σαν μια δεύτερη οικογένεια, τον αποχαιρέτησε με βαθιά θλίψη και αίσθημα κενού.

Ο Γεώργιος Καπρίνης, μια χαρισματική και πολυσχιδής προσωπικότητα, γεννήθηκε το 1943 στην Κοζάνη και είχε την τραγική μοίρα να μη γνωρίσει τον πατέρα του που σκοτώθηκε όσο η μητέρα του εγκυμονούσε. Γι' αυτό και έγραφε το όνομά του προσθέτοντας πάντα τα αρχικά Στ[έργιος] του πατρωνύμου του, που δεν ξεχνούσε ούτε στην υπογραφή του.

Στα δύσκολα χρόνια της μεταπολεμικής Ελλάδας η μητέρα του Κλεονίκη αφοσιώθηκε απόλυτα στη φροντίδα και ανατροφή του. Εγκαταστάθηκαν στη Θεσσαλονίκη όπου φοίτησε στο Α΄ Πρότυπο Δημοτικό Σχολείο και ακολούθως στο Πειραματικό Γυμνάσιο Θεσσαλονίκης. Ήταν περήφανος για το σχολείο του και αναφερόταν πάντα με σεβασμό στους καθηγητές του.

Σπούδασε στην Ιατρική Σχολή του Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης και επέλεξε να ειδικευθεί στη Νευρολογία-Ψυχιατρική. Ακολούθως μετεκπαιδεύτηκε επί 3 χρόνια στο Παρίσι, ως υπότροφος του ΙΚΥ και της Γαλλικής Κυβερνήσεως, σε πρωτοπόρα για την εποχή επιστημονικά πεδία. Τις νέες γνώσεις του μετέφερε στην Ελλάδα μέσα από την ένταξή του στην ακαδημαϊκή ψυχιατρική, όπου ανήλθε όλες τις βαθμίδες της πανεπιστημιακής ιεραρχίας μέχρι τη βαθμίδα του Καθηγητή.

Για μια 20ετία υπήρξε διευθυντής δύο Πανεπιστημιακών Κλινικών, αρχικά της Α΄ Πανεπιστημιακής Ψυχιατρικής Κλινικής και ακολούθως, από το 1998, της Γ΄ Πανεπιστημιακής Ψυχιατρικής Κλινικής, από όπου και αφυπηρέτησε το 2010.

Στην ακαδημαϊκή του πορεία, τον Γεώργιο Καπρίνη χαρακτήριζαν πρωτίστως οι βαθιές ψυχιατρικές γνώσεις του και το μέγιστο ενδιαφέρον του για τους ασθενείς. Ήταν ένας χαρισματικός δάσκαλος που χαιρόταν να δέχεται ερωτήσεις και απορίες, να προκαλεί την αμφισβήτηση και να συζητά. Στον ερευνητικό τομέα εξέπληττε πάντα με τις ιδέες του, ήταν ανοιχτός σε καινοτόμες προτάσεις, ωθώντας τους συνεργάτες του σε νέα επιστημονικά πεδία και πρωτοπόρες έρευνες και υπηρεσίες. Ελεύθερο πνεύμα, είχε το χάρισμα να συνθέτει αντίθετες απόψεις και προσεγγίσεις, από την αντιψυχιατρική έως την κλασική «οργανική» ψυχιατρική, χωρίς αποκλεισμούς, χωρίς επιστημονικές ιδεοληψίες. Συνεργάτες και μαθητές του έχουν σήμερα ανελιχτεί επιστημονικά σε υψηλές θέσεις της ακαδημαϊκής ψυχιατρικής, ως επίλεκτα μέλη της ψυχιατρικής κοινότητας.

Όντας ανήσυχη και πολυσχιδής προσωπικότητα, δεν μπορούσε παρά να συμμετέχει στα κοινά. Σημαντική και ουσιαστική ήταν η παρουσία του στα όργανα διοίκησης της Ιατρικής Σχολής. Υπήρξε από τους λίγους Καθηγητές

που ήταν συνεχώς μέλη της Γενικής Συνέλευσης της Ιατρικής Σχολής, από την καθιέρωση του θεσμού (1982) έως την αφυπηρέτησή του. Διετέλεσε Διευθυντής του Τομέα Νευροεπιστημών για περισσότερα από 10 έτη. Συμμετείχε σε πλήθος επιτροπών τόσο της Ιατρικής Σχολής όσο και του Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης, συμβάλλοντας ουσιαστικά στο έργο τους και αφήνοντας το προσωπικό του στίγμα. Ιδρυτικό μέλος του συνδικαλιστικού οργάνου της Σχολής, του «Συλλόγου μελών ΔΕΠ της Ιατρικής Σχολής ΑΠΘ», διετέλεσε επί μία 10ετία πρόεδρος του συλλόγου, αγωνιζόμενος για την προώθηση και επίλυση των προβλημάτων των πανεπιστημιακών ιατρών.

Σημαντική ήταν η συμβολή του Γιώργου Καπρίνη στην προώθηση της Ψυχιατρικής Μεταρρύθμισης στην Ελλάδα. Ως πρόεδρος της Επιτροπής Ψυχικής Υγείας του Υπουργείου Υγείας σχεδίασε, οργάνωσε και διηύθυνε, στις αρχές της δεκαετίας του 1990, την παρέμβαση στο Ψυχιατρικό Νοσοκομείου Λέρου για την αποασυλοποίηση των ασθενών και τη μεταφορά τους σε ξενώνες στους τόπους καταγωγής τους. Συνέχισε να συμμετέχει μέχρι τον θάνατό του στις προσπάθειες για την αποασυλοποίηση, την ψυχοκοινωνική αποκατάσταση των ασθενών και την ανάπτυξη εξωνοσοκομειακών δομών μέσω της μη κυβερνητικής εταιρείας ΕΨΥΚΑ. Η συμβολή του στην προώθηση της Ψυχιατρικής Μεταρρύθμισης στη χώρα μας δυστυχώς δεν έχει αναγνωριστεί στον βαθμό που θα έπρεπε.

Σε όλη του τη ζωή, ο Γιώργος Καπρίνης είχε δίπλα του, σύντροφο και συμπαραστάτη του, την αγαπητή συνάδελφο Ομότιμη Καθηγήτρια της Ιατρικής Σχολής του ΑΠΘ Ελευθερία Κουρίλα-Καπρίνη. Τους συνέδεε μια βαθιά συναισθηματική σχέση που ξεκίνησε από τα φοιτητικά τους χρόνια και συνεχίστηκε μέχρι τέλους. Ήταν ο στυλοβάτης και ο φύλακας άγγελός του. Ευτύχησαν να δουν μαζί τους δύο γιούς τους επιστημονικά και επαγγελματικά καταξιωμένους. Τον Στέργιο Επίκουρο Καθηγητή Ψυχιατρικής στο ΑΠΘ και τον Σπύρο να σταδιοδρομεί ως αρχιτέκτονας στη Μεγάλη Βρετανία. Ο χρόνος ας απαλύνει τη θλίψη και τον πόνο τους για την ξαφνική απώλεια.

Μετά την αφυπηρέτησή του ο Γεώργιος Καπρίνης δεν αποσύρθηκε αλλά παρέμεινε επιστημονικά ενεργός. Συνέχισε να συμμετέχει στις επιστημονικές εκδηλώσεις, να δημιουργεί και να υπηρετεί την εκπαίδευση των νέων συναδέλφων με κάθε ευκαιρία, μεταδίδοντας πλέον τη μακρόχρονη εμπειρία του και τη σοφία του. Αναλογίζομαι ακόμη την τελευταία του ομιλία στο πρόσφατο Πανελλήνιο Ψυχιατρικό Συνέδριο στη Λάρισα που μας καθήλωσε με τη διεισδυτική και διαλεκτική του σκέψη.

Πριν από έναν χρόνο δημοσίευσε το τελευταίο πόνημά του, που δεν ανήκε στον χώρο της ψυχιατρικής, αλλά της ποίησης. Εξέδωσε την ποιητική συλλογή «Εγώ ο άλλος» σε μία συγκινητική και καλαίσθητη έκδοση με την εικαστική βοήθεια του γιου του, Σπύρου. Μας φανέρωσε μία ακόμη πλευρά του εαυτού του, της ψυχής του, που ίσως επιμελώς έκρυβε τα προηγούμενα χρόνια. Ώριμος μετά από μια μακρά διαδρομή με δράση, γνώση και επιτυχία, έγραφε:

Τη ζωή, ζωή τη λένε
μα έργο της ο θάνατος.
Η μεγάλη ακίνητη δεξαμενή
που μας περιμένει.
Πρόβλημα δεν είναι ο θάνατος...

Για να συμπληρώσει σ' ένα επόμενο ποίημα του:

Τώρα χειμώνας πια,
δεν φοβάμαι τίποτε,
κι' οι νοσταλγίες ξεθώριασαν πια κι' αυτές.
Είμαι, σχεδόν, ελεύθερος.

Το τέλος δεν βρήκε τον Γιώργο Καπρίνη, αυτόν τον δάσκαλο και ιατρό, απροετοίμαστο. Ήταν από καιρό έτοιμος. Εμάς μας τάραξε ο θάνατός του.

Καλό σου ταξίδι Γιώργο. Οι φίλοι σου, οι συνεργάτες σου, οι μαθητές σου, οι Καθηγητές της Ιατρικής Σχολής του ΑΠΘ θα σε θυμόμαστε για πάντα.

Ιωάννης Νηματούδης
Καθηγητής Ψυχιατρικής ΑΠΘ
Διευθυντής Γ΄ Ψυχιατρικής Κλινικής ΑΠΘ

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  Tel: (+30) 210-74 62 577
  Fax: (+30) 210-74 62 554
  E-mail: cdalla@med.uoa.gr
  Website: scholar.uoa.gr/cdalla

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  E-mail: n.loza@behman.com
  Website: www.wfmh2015.com

- **17th International Conference on Philosophy, Psychiatry and Psychology "Why do humans become mentally ill? Anthropological, biological and cultural vulnerabilities of mental illness", Frutillar, Chile**
  29–31 October 2015
  Organizers: (1) Centro de Estudios de Fenomenologia y Psychiatria, Universitad Diego Portales, Chile, (2) International Network for Philosophy and Psychiatry Collaboration, (3) European Psychiatric Association/Philosophy Section
  Contact: Dr Leonor Irarrazaval
  E-mail: centrodefenomenologia@mail.udp.cl
  Website: www.centrodefenomenologia.udp.cl

- **12th Congress of World Association for Psychological Rehabilitation, Seoul, Korea**
  1–4 November 2015
  Organizers: (1) World Association for Psychological Rehabilitation (WARP), (2) Korean Association for Psychological Rehabilitation (KARP)
  Contacts: (1) Dr Afzal Javed, (2) Prof. Tae-Yeon Hwang
  Congress Secretariat: Nina Wilson
  E-mail: afzal.javed@ntlworld.com, ilymh@gmail.com
  Website: www.iwarp.info

- **3rd Congress of Preventive Psychiatry and 4th Psychiatric Congress of Eastern Europe "Preventive Psychiatry & Psychiatry in Eastern Europe", Athens, Greece**
  12–15 November 2015
  Organizer: Society of Preventive Psychiatry

Collaboration: (1) Psychiatric Association for Eastern Europe and the Balkans (PAEEB), (2) Hellenic Psychiatric Association (HPA)
Contact Prof. George N. Christodoulou
Congress Secretariat: CONVIN
29, K. Varnali street, GR-152 32 Chalandri
Prefecture of Attica, Athens, Greece
Tel: (+30) 210-68 33 600, 210-72 14 184
Fax: (+30) 210-72 42 032
E-mail: (a) profgchristodoulou@gmail.com, (b) psych@psych.gr
Website: www.preventive-psychiatry2015.com

- **WPA International Congress of Psychiary, Taipei, Tawan**
  18–22 November 2015
  Organizer: World Psychiatric Association
  Congress Secretariat: c/o Elite Professional Conference Organizer
  4F, No 285, Sec 2, Tiding Boulevard, Taipei, 114, Taiwan
  Tel: (+88) 62 2798 6225
  Fax: (+88) 62 2798 6225
  E-mail: secretariat@wpaic2015.tw
  Website: www.wpaic2015.tw

- **15th Internationa forum on mood and anxiety disorders (IFMAD 2015), Prague, Czech Republic**
  2–4 December 2015
  Organizers: International Forum on Mood and Anxiety disorders (IFMAD)
  Congress Secretariat: Publi Creations
  74 Boulevard d' Italie, 980 00 MONACO
  Tel: (+377) 97 97 35 55
  Fax: (+377) 97 97 35 50
  E-mail: ifmad@publicreations.com
  Website: www.ifmad.org/2015/

- **24th European Congress of Psychiatry, Madrid, Spain**
  12–15 March 2016
  Organizer: European Psychiatric Association
  Congress Secretariat: Kenes International Organizers of Congresses SA
  7, rue Francois-Versonnex, CP 6053
  1211 Geneva 6, Switzerland
  Tel: (+4122) 508 7599
  Fax: (+4122) 906 9140
  E-mail: invitation@kenes.com
  Website: www.europsychiatric.com

- **WPA International Congress "Integrating clinical, community and public health in psychiatry", Istanbul, Turkey**
  6–10 July 2016
  Organizers: (1) Psychiatric Association of Turkey, (2) Turkish Neuropsychiatric Society
  Contact: Dr Levent Kuey
  E-mail: kueyl@superonline.com
  Website: www.wpainstanbul2016.org

- **"Psychiatry: Integrative Care for the Community", Cape Town, South Africa**
  18–22 November 2016
  Organizers: (1) World Psychiatric Association (WPA), (2) South African Society for Psychiatrists (SASOP)
  Congress Secretariat Scatterlings Conferences and events
  Tel: (+27) 11 463 5085
  Fax: (+27) 11 463 3265
  E-mail: Bernard.sasop@mweb.co.za
  Website: www.wpacapetown2016.org.za, www.soafrica.com

- **WPA World Congress of Psychiatry "`Psychiatry of the 21st Century: Context, Controversies and Commitment", Berlin, Germany**
  8–12 October 2017
  Organizer: German Association for Psychiatry, Psychotherapy and Psychosomatics
  Contact: Prof Peter Falkai
  E-mail: wpa2017@cpo0-hanser.de
  Website: www.wpaberlin2017.com