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Editorial
Άρθρο Σύνταξης

Psychosis risk syndrome: Pharmacological interventions

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The potential benefits of providing effective treatment for young people at psychosis risk syndrome (PRS) –known variably as ultra high risk (UHR)– of developing a psychotic disorder has been recognized only the last decade. Interventions on this phase, which can be divided to psychosocial and pharmacological, aim to reduce symptom severity, as well as to delay or even to fully prevent the onset of psychosis.

There are few published studies to date that have studied the use of medications in PRS. As antipsychotics are helpful in the treatment and relapse prevention for psychosis, these drugs have been tried for the PRS individuals. According to the first published study, a randomized controlled trial (RCT), UHR subjects receiving Cognitive Behavior Therapy (CBT) and a low dose of risperidone for 6 months, manifested significantly lower rate of transition to psychosis (9.7%) compared to UHR subjects receiving supportive psychotherapy (36%). However, in subsequent follow ups (f.u.), 6 months and 3–4 years later, this significant difference had been disappeared.[1] Another RCT double blind study, comparing olanzapine to placebo, reached similar results[2] while two open label studies found significant improvement on both several symptom dimensions and functioning at the end of 8 and 12 weeks of treatment with aripiprazole and amisulpride correspondingly.[3] Furthermore, a naturalistic multisite study reported that antipsychotics improve positive attenuated symptoms and disorganized behavior in PRS subjects but did not influence negative and general symptoms, while antidepressants did not decline symptom severity.[4] Finally, according to the latest published RCT double blind study,[5] UHR individuals who received cognitive therapy plus a low dose of risperidone or cognitive therapy plus placebo or supportive psychotherapy plus placebo for 6 months, did not manifest any difference both in symptom improvement and conversion rate to psychosis.

In summary, from all the above studies, one can assume that intervention with antipsychotic medication in PRS subjects may delay conversion to psychosis and improve symptoms, especially positive symptoms, during the active phase of treatment, but there is no evidence of long lasting effects after therapy termination.

There are a number of reasons against the use of antipsychotics in PRS individuals. First of all there are potentially serious side effects associated with all antipsychotic drugs such as extrapyramidal symptoms, metabolic syndrome, sexual dysfunction etc. In addition, many UHR subjects, as they have strange experiences, are concerned that they are going "mad". The prescription of drugs with indications for schizophrenia and other psychotic disorders increases the distress and make them feel stigmatized, especially if it occurs without information about potential benefits. Finally, of concern is recent evidence that long term use of antipsychotics,

even in low doses, can cause sensitization of dopamine receptors, leading to rapid-onset psychosis following treatment termination.

Apart from the previously mentioned naturalistic study,[4] two other open label studies examined the effect of antidepressants on PRS subjects and found a significantly lower rate of conversion to psychosis compared to antipsychotics.[6] It has been suggested that depression increases the likelihood that prodrome anomalous experiences develop into a psychotic disorder. Thus, antidepressants may have a protective effect by improving mood and reducing the individual's faulty appraisal of prodromal symptoms.[3] In addition, antidepressants may modulate the person's response to environmental stressors. Stress has been linked with both the onset and relapse of psychosis by an overactivity of the hypothalamus-pituitary-adrenal (HPA) axis. According to the one and only RCT double blind study, ω-3 had a significantly superior beneficial effect both on conversion rate to psychosis and improvement of symptomatology and functioning compared to placebo.[7] The most important finding of that study is that group differences were sustained after cessation of interventions. Trials with antipsychotics have not found this. Furthermore, the researchers reported high consent rate, low drop-out rate and non group differences regarding side effects, indicating that this treatment is well tolerated. Omega-3 fatty acids have neuroprotective properties by inducing antiapoptotic and antioxidative factors.[7] It was found that eicosapentaenoic acid (EPA) increases glutathione, the brain's principal antioxidant defense. There are findings supporting that acute psychosis is related with glutathione deficiency.[6] There is also evidence that ω-3 have a generalized positive effect on mental health. Controlled trials reported beneficial effects in depression, bipolar disorder, borderline personality disorder, antisocial behavior/aggression, attention deficit/hyperactivity disorder (ADHD) and autism, suggesting that ω-3 modulate mood, impulsivity and aggression.[6]

There is a continuing research interest on the field of pharmacological intervention in PRS subjects. There are several ongoing studies, most of them double-blind, placebo-controlled trials. Three of them intend to compare antipsychotic drugs i.e. ziprasidone, quetiapine, aripiprazole to placebo and another one tests the effect of ω-3. Finally, two other studies investigate the influence of D –serine and sarcosine-substances involved in the glutamate pathways– compared to placebo.

In conclusion, research on early intervention for UHR individuals is still in its infancy. Current scientific data suggest that the "clinical staging model"[6] of care should be followed. Intervention should begin with the more benign treatments such as psychosocial and/or omega-3 fatty acids as a first step, by progressing to more intensive interventions for patients who do not improve. Depression and anxiety are highly prevalent in UHR subjects and represent a key treatment target in their own right. In these cases prescription of antidepressants should be considered. On the contrary, antipsychotic medication should not be considered as a first treatment option. However, a rapid worsening of psychotic symptoms together with significant decrease in functioning are indices suggesting prescription of a 2nd generation antipsychotic at low dose.

Future research is needed. A main research effort should be focused to indentify those within the UHR population who are at greatest risk to develop a frank psychosis. The achievement of this aim includes among others: (1) Improvements in diagnostic tools. (2) To find out if there is a relationship between the presence/absence of individual symptoms or clusters of symptoms and remission or progression of PRS. (3) Use of laboratory findings such as neuroimaging findings. For instance, it is suggested that PRS subjects who later developed psychosis had less gray matter volume in specific brain areas than those who did not. In addition, there are some questions which should be answered[6] such as for how long should treatment continue? Or can interventions during PRS modify the outcome if the full blown psychosis develops? etc.

It is evident that UHR population is a heterogenous clinical population at risk not only for schizophrenia but also other mental health problems[6] such as depression, anxiety, substance abuse etc. In addition, they have

cognitive, social and vocational difficulties. Although most of them will not develop psychosis, they are not well and they need help, especially as adolescence and early adulthood are crucial periods regarding personal growth and development of academic, social and occupational skills. Developing effective intervention strategies will provide therapy of existing distress and disability in addition to introducing the possibility of delaying or preventing the onset of a psychotic disorder.[6]

Key words: psychosis, risk syndrome, pharmacological interventions

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Άρθρο Σύνταξης
Editorial

Σύνδρομο κινδύνου για ψύχωση: Φαρμακολογικές παρεμβάσεις

Ψυχιατρική 2011, 22:277–282

Τα οφέλη της παροχής αποτελεσματικής θεραπείας σε νέα άτομα που βρίσκονται σε κατάσταση η οποία ονομάζεται «σύνδρομο κινδύνου για ψύχωση» (psychosis risk syndrome) –εναλλακτικά είναι γνωστά και ως άτομα «πολύ αυξημένου κινδύνου» (UHR) για ψύχωση– έχουν αναγνωρισθεί μόλις την τελευταία δεκαετία. Οι παρεμβάσεις σ' αυτή τη φάση, οι οποίες μπορεί να διαχωρισθούν αδρά σε ψυχοκοινωνικές και φαρμακολογικές, έχουν ως στόχο τη μείωση της βαρύτητας των συμπτωμάτων αλλά και την καθυστέρηση ή, αν είναι δυνατόν, την αποτροπή της ανάδυσης της ψύχωσης.

Μέχρι σήμερα υπάρχουν λίγες δημοσιευμένες μελέτες που διερευνούν τις φαρμακολογικές παρεμβάσεις σε σύνδρομο κινδύνου για ψύχωση (ΣΚΨ). Μία πρώτη ομάδα φαρμάκων των οποίων η επίδραση μελετήθηκε ήταν τα αντιψυχωτικά, τα οποία όπως είναι γνωστό ασκούν θεραπευτική δράση στις ψυχωτικές διαταραχές αλλά προλαμβάνουν και τις υποτροπές. Σύμφωνα με την πρώτη δημοσιευθείσα τυχαιοποιημένη μελέτη με ομάδα ελέγχου (ΤΜΟΕ), τα άτομα σε ΣΚΨ που έλαβαν γνωσιακή συμπεριφορική θεραπεία (ΓΣΘ) και μικρή δόση ρισπεριδόνης για 6 μήνες, ανέπτυξαν σε σημαντικά μικρότερο ποσοστό ψύχωση (9,7%) σε σύγκριση μ' εκείνα που έλαβαν υποστηρικτική ψυχοθεραπεία (36%). Σε δύο όμως επόμενες επανεκτιμήσεις 6 μήνες και 3–4 έτη αργότερα η σημαντική αυτή διαφορά εξαφανίσθηκε.[1] Παρόμοια είναι και τα ευρήματα μιας άλλης διπλής τυφλής, ΤΜΟΕ μελέτης που συνέκρινε την ολανζαπίνη με το εικονικό φάρμακο (ΕΦ), ενώ δύο άλλες ανοιχτές μελέτες αναφέρουν σημαντική βελτίωση τόσο σε διάφορα πρόδρομα συμπτώματα όσο και στη λειτουργικότητα στο τέλος 8 και 12 εβδομάδων θεραπείας με αριπιπραζόλη και αμισουλπρίδη αντίστοιχα.[3] Επιπρόσθετα, μία νατουραλιστική μελέτη σημειώνει ότι τα αντιψυχωτικά βελτιώνουν τα εξασθενημένα θετικά συμπτώματα και την αποδιοργανωμένη συμπεριφορά, δεν ασκούν όμως καμία επίδραση στα αρνητικά και στα γενικά συμπτώματα ενώ τα αντικαταθλιπτικά δεν επιφέρουν μείωση της βαρύτητας των συμπτωμάτων σε καμία διάστασή τους.[4] Τέλος, σύμφωνα με την πιο πρόσφατη διπλή τυφλή, ΤΜΟΕ, μελέτη άτομα που έλαβαν γνωσιακή θεραπεία (ΓΘ) συν μικρή δόση ρισπεριδόνης ή ΓΘ συν ΕΦ ή υποστηρικτική ψυχοθεραπεία συν ΕΦ για 6 μήνες, δεν εμφάνισαν καμία διαφοροποίηση μεταξύ τους τόσο ως προς τη βελτίωση της συμπτωματολογίας όσο και ως προς το ποσοστό ανάπτυξης ψύχωσης.[5]

Συνοπτικά, από όλες τις ανωτέρω μελέτες μπορεί κανείς να συμπεράνει ότι τα αντιψυχωτικά σε ΣΚΨ μπορεί να καθυστερούν την έναρξη της ψύχωσης και να βελτιώνουν τα συμπτώματα, κυρίως τα θετικά, κατά τη διάρκεια της θεραπείας, δεν ασκούν όμως μακροπρόθεσμη προστατευτική δράση μετά τον τερματισμό της.

Υπάρχουν αρκετοί λόγοι για τη μη χρήση αντιψυχωτικών σε ΣΚΨ. Πρώτα από όλα, η πιθανότητα εμφάνισης παρενεργειών όπως τα εξωπυραμιδικά συμπτώματα, το μεταβολικό σύνδρομο, η σεξουαλική δυσλειτουργία κ.λπ. Επιπρόσθετα, τα άτομα αυτά επειδή βιώνουν διάφορες «παράξενες» εμπειρίες ανησυχούν ότι πιθανώς «τρελαίνονται». Η συνταγογράφηση φαρμάκων με ενδείξεις τη σχιζοφρένεια και άλλες ψυχωτικές διαταραχές αυξάνει την ανησυχία και το άγχος, ιδίως αν η συνταγογράφηση δεν συνοδεύεται από ενημέρωση για τα πιθα-

νά οφέλη της θεραπευτικής προσπάθειας. Τέλος, υπάρχουν αναφορές που υποστηρίζουν ότι η μακροχρόνια χρήση αντιψυχωτικών προκαλεί ευαισθητοποίηση των υποδοχέων της ντοπαμίνης, γεγονός που μπορεί να οδηγήσει σε ταχεία ανάπτυξη ψύχωσης μετά τον τερματισμό της θεραπείας.

Εκτός από την προαναφερθείσα νατουραλιστική μελέτη,[4] υπάρχουν δύο άλλες ανοιχτές μελέτες που διερευνούν την επίδραση των αντικαταθλιπτικών φαρμάκων σε άτομα με ΣΚΨ και βρίσκουν σημαντικά μικρότερο ποσοστό ανάδυσης ψύχωσης συγκριτικά με τα αντιψυχωσικά.[6] Αναφέρεται ότι η ύπαρξη κατάθλιψης αυξάνει την πιθανότητα οι πρόδρομες, περίεργες εμπειρίες, που βιώνουν άτομα σε ΣΚΨ να εξελιχθούν σε ανοιχτή ψυχωτική διαταραχή. Τα αντικαταθλιπτικά είναι πιθανό να ασκούν προστατευτική δράση βελτιώνοντας τη διάθεση και μειώνοντας έτσι την εσφαλμένη εκτίμηση που έχει το άτομο για τα βιώματα αυτά.[3] Επιπρόσθετα, τα αντικαταθλιπτικά μπορεί να ρυθμίζουν και την απάντηση του ατόμου σε περιβαλλοντικούς στρεσογόνους παράγοντες. Το στρες συνδέεται τόσο με την έναρξη όσο και με την υποτροπή μιας ψυχωτικής διαταραχής μέσω υπερδραστηριότητας του άξονα υποθάλαμος-υπόφυση-επινεφρίδια (ΥΥΕ).

Μια τρίτη θεραπευτική επιλογή είναι η χρήση ωμέγα-3 (ω-3) λιπαρών. Σύμφωνα με τη μόνη διπλή τυφλή, ΤΜΟΕ που υπάρχει, τα ω-3 λιπαρά είχαν σημαντικά μεγαλύτερο ευνοϊκό αποτέλεσμα τόσο όσον αφορά το ποσοστό ανάπτυξης ψύχωσης όσο και ως προς τη βελτίωση της πρόδρομης συμπτωματολογίας και της λειτουργικότητας σε σύγκριση με το ΕΦ.[7] Το πιο σημαντικό εύρημα της μελέτης ήταν η διατήρηση των διαφορών μεταξύ των δύο ομάδων μετά την ολοκλήρωση της θεραπευτικής παρέμβασης, στοιχείο που δεν ανευρίσκεται σε καμία μελέτη που χρησιμοποίησε αντιψυχωτική αγωγή. Ακόμη, δεν υπήρχαν διαφορές ως προς τις παρενέργειες, υπήρχε υψηλό ποσοστό συμφωνίας συμμετοχής (consent rate) και χαμηλό ποσοστό διακοπής της θεραπείας, στοιχεία που καταδεικνύουν ότι η θεραπεία με ω-3 είναι πολύ καλά ανεκτή. Τα ω-3 λιπαρά έχουν νευροπροστατευτικές ιδιότητες διότι κινητοποιούν αντι-αποπτωτικούς και αντιοξειδωτικούς παράγοντες.[7] Υποστηρίζεται ότι αυξάνουν τη γλουταθειόνη, την κύρια αντιοξειδωτική άμυνα του εγκεφάλου, έλλειψη της οποίας σχετίζεται με την εμφάνιση οξείας ψύχωσης.[6] Τα ω-3 φαίνεται ότι ασκούν μια θετική επίδραση στην ψυχική υγεία γενικά, μια και υπάρχουν μελέτες που αναφέρουν ευνοϊκά αποτελέσματα στην κατάθλιψη, τη διπολική διαταραχή, τη μεταιχμιακή διαταραχή προσωπικότητας, την αντικοινωνική συμπεριφορά/επιθετικότητα, τη διαταραχή ελλειμματικής προσοχής/υπερκινητικότητα και τον αυτισμό, στοιχεία που υποδηλώνουν ότι τα ω-3 δρουν ρυθμίζοντας τη διάθεση, την παρορμητικότητα και την επιθετικότητα.[6]

Το ερευνητικό ενδιαφέρον αναφορικά με τις φαρμακολογικές παρεμβάσεις σε άτομα που βρίσκονται σε ΣΚΨ συνεχίζεται αμείωτο. Υπάρχουν αρκετές μελέτες σε εξέλιξη, οι περισσότερες διπλές τυφλές. Τρεις από αυτές έχουν ως στόχο να συγκρίνουν αντιψυχωτικά φάρμακα όπως η ζιπρασιδόνη, η κουετιαπίνη και η αριπιπραζόλη με ΕΦ, ενώ μία τέταρτη διερευνά, συγκριτικά με το ΕΦ, την επίδραση των ω-3. Τέλος, άλλες δύο μελέτες διερευνούν τη δράση της D-σερίνης και της σαρκοσίνης, ουσιών που εμπλέκονται στις γλουταμινεργικές οδούς, σε σύγκριση με το ΕΦ.

Η έρευνα αναφορικά με την πρώιμη παρέμβαση σε άτομα με ΣΚΨ είναι ακόμη στα σπάργανα. Τα μέχρι σήμερα δεδομένα υποδεικνύουν ότι καλό είναι να ακολουθείται το «μοντέλο κλινικών σταδίων» (clinical staging model).[6] Οι αρχικές θεραπευτικές παρεμβάσεις θα πρέπει να είναι πιο ήπιες, όπως οι ψυχοκοινωνικές ή η χορήγηση ω-3, και στη συνέχεια να εφαρμόζονται πιο «επιθετικές» στα άτομα που δεν βελτιώνονται. Για την κατάθλιψη και το άγχος, που συχνά υπάρχουν στα άτομα αυτά, μπορεί κανείς να σκεφτεί τη συμπτωματική αντιμετώπιση με αντικαταθλιπτικά. Αντίθετα, τα αντιψυχωτικά δεν θα πρέπει να αποτελούν την πρώτη θεραπευτική επιλογή. Μία όμως ταχεία επιδείνωση των ψυχωτικών πρόδρομων συμπτωμάτων μαζί με σημαντική έκπτωση της λειτουργικότητας αποτελούν ενδείξεις για τη χορήγηση αντιψυχωτικών 2ης γενιάς σε μικρή δόση.

Απαιτείται περαιτέρω ερευνητική προσπάθεια, με πρώτο στόχο την ανίχνευση μέσα στον συνολικό πληθυσμό των ατόμων που βρίσκονται σε ΣΚΨ εκείνων που βρίσκονται στον μέγιστο κίνδυνο για ανάδυση ψύχωσης. Για την επίτευξη του σκοπού αυτού θα πρέπει οι έρευνες να στοχεύουν μεταξύ άλλων: (1) Στη βελτίωση των διαγνωστικών εργαλείων. (2) Στη διερεύνηση της πιθανής συσχέτισης μεταξύ παρουσίας/απουσίας συγκεκριμένων συμπτωμάτων ή ομάδων συμπτωμάτων με την επιδείνωση/ύφεση του ΣΚΨ. (3) Στην αξιοποίηση εργαστηριακών ευρημάτων όπως π.χ. τα νευροαποικονιστικά ευρήματα. Υπάρχουν μελέτες που αναφέρουν ότι τα άτομα με ΣΚΨ που εμφάνισαν μετέπειτα ψύχωση είχαν πριν την εμφάνισή της μικρότερο όγκο φαιάς ουσίας σε

συγκεκριμένες περιοχές του εγκεφάλου από άτομα που δεν ανέπτυξαν ψύχωση. Επιπρόσθετα, υπάρχουν και πολλές ερωτήσεις που χρήζουν απάντησης, όπως για παράδειγμα για πόσο χρονικό διάστημα θα πρέπει να συνεχίζεται η θεραπεία ή αν οι παρεμβάσεις στο ΣΚΨ μπορεί να τροποποιούν την πρόγνωση και έκβαση μιας μελλοντικά αναδυόμενης ψύχωσης κ.λπ.

Ο συνολικός αριθμός των ατόμων που βρίσκονται σε ΣΚΨ είναι ένας ετερογενής πληθυσμός για τον οποίο υπάρχει κίνδυνος όχι μόνον για σχιζοφρένεια αλλά και για άλλες διαταραχές όπως καταθλιπτικές, αγχώδεις, κατάχρηση ουσιών κ.λπ., ενώ επιπρόσθετα τα άτομα αυτά παρουσιάζουν γνωστικές, κοινωνικές και επαγγελματικές δυσκολίες. Αν και πολλοί δεν θα αναπτύξουν ψύχωση στο μέλλον, εντούτοις δεν είναι καλά και χρειάζονται άμεση βοήθεια, δεδομένου ότι πρόκειται για άτομα που βρίσκονται στην εφηβεία ή νωρίς στην ενήλικη ζωή, σε περιόδους δηλαδή κρίσιμες για την προσωπική τους ολοκλήρωση και την ανάπτυξη κοινωνικών δεξιοτήτων, εκπαιδευτικών και επαγγελματικών. Η ανάπτυξη αποτελεσματικών στρατηγικών παρέμβασης θα προσφέρει θεραπεία στα υπάρχοντα συμπτώματα και ελλείμματα, ενώ υπάρχει η προοπτική της καθυστέρησης της εμφάνισης ή και της πρόληψης της ανάδυσης κάποιας ψυχωτικής διαταραχής.[6]

Λέξεις ευρετηρίου: ψύχωση, σύνδρομο κινδύνου, φαρμακολογικές παρεμβάσεις

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Special article
Ειδικό άρθρο

Advances and perspectives in mental health: Is psychiatry being stigmatized?

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The specialty of Psychiatry and the interdisciplinary work performed by psychiatrists in conjunction with other scientific and humanistic disciplines is being affected by some facts which ead to its stigmatization. There are both internal and external risks that are affecting the profession. Among the internal ones we may mention the differents diagnostic criteria used by psychiatrists and the differences between treatments – as there is a wide variety of treatment options. Besides, the practice of psychiatry may differ enormously, according to the perspective –biological, psychological, social, cultural, and so on– of each psychiatrist. The internal inconsistencies give rise to some of the external risks psychiatry and psychiatrists have to face: patients' discontent or even mistrust, the intrusion of other professions in the field of psychiatry and the negative image psychiatry has among the public. Just as it occurred in many other places before, the passing of a new mental health law in Argentina has proved to be an occasion for deep debate. The passing of this law has caused big controversy, especially among professional associations, private mental health services, NGOs which represent users and their families, trade unions which represent health workers, political and economic decision makers, etc. In Argentina, the debate of ideas has always been rich. Even when political parties were forbidden, there were discussions taking place among groups which supported psychoanalytic and psychodynamic approaches. There are many who demonize the developments made in the field of psychiatry and they also campaign against such developments. They catch the public's attention and they convince legislators, thus spreading the idea that psychiatry may be dangerous. As a consequence, for example, the new law gives similar status to psychiatrists and psychologists when it states that the decision to confine a patient into hospital "should be signed by two professionals, one of whom should be either a psychologist or a psychiatrist". We all know that psychologists play a very important role in mental health care, but the medical training of psychiatrists will surely enable them to make very complex medical decisions such as the decision to confine a patient into hospital. Some other aspects to be mentioned about this law are that no reference is made to outpatient services, although they are of utmost importance in everyday practice, and that there is a bureaucratization of hospitaliza-

tion. Such decision is no longer made by a professional, as a means to achieve the best treatment possible, but by a judge, who is expected to know what is best for the patient. However, there are basic contents in this law which are definitely positive: it defends patients' rights; it promotes interdisciplinary team work; it recommends deinstitutionalization, community services and, if necessary, inpatient services in general hospitals. However, there are many doubts as regards the way this will be put into practice. In most countries psychiatry is also threatened by a shortage of psychiatrists. In Argentina, the number of medical students who choose this branch of medicine as their specialty has declined the past twenty years, while the number of prospective psychologists has soared in the meantime. These are some of the reasons why many believe that psychiatry is being discredited. In this scenario, where there are both internal and external risks for psychiatry, our main professional interest is basedon improving our patients' quality of life, which obviously includes their mental health. In order to achieve the best results we should avoid militant attitudes and the ideologization of reality, and be as creative as possiblelooking for the best way to do so.

Key words: mental health, stigma, advances, perspectives

In spite of the during many advances there have been in psychiatry in the past decades, the specialty is now facing a paradoxical situation: we find that psychiatry – namely the interdisciplinary work performed by psychiatrists in conjunction with other scientific and humanistic disciplines, other medical specialties and the mental health sphere– is being affected by some facts which lead to its stigmatization. As H. Katschnig mentioned in the forum "Are Psychiatrists an Endangered Species?",[1] I believe there are both internal and external risks that are affecting the profession. Among the internal ones we can mention the differents diagnostic criteria used by psychiatrists –which may make patients doubt about their condition, and the differences between treatments –as there is a wide variety of treatment options. On top, many psychiatrists may feel that they do not know enough about medications, as many might suspect the information received about them is biased. Besides, the practice of psychiatry may differ enormously according to the perspective –biological, psychological, social, cultural, and so on– of each psychiatrist. This may occur due to the fact that individual psychiatrists work in a limited setting and have specific experience on a limited number of cases, so each psychiatrist comes to specific conclusions about his/her field of knowledge, and contrasting ideas may arise. These internal inconsistencies give rise to some of the external risks psychiatry and psychiatrists have to face: patients' discontent or even mistrust, the intrusion of other professions in the field of psychiatry and the negative image psychiatry has among the public.

However, there are some psychiatrists who believe there should be only one psychiatry, although there may be different branches –due to super-specialization– and that this is a psychiatry which is based on the person. It seems that a holistic understanding of the patient has become a need: they are people who suffer from disorders with biological, psychological, social, cultural and spiritual implications, but all these aspects concern a specific person and it is from this perspective that psychiatry and mental health professionals have to treat their patients: as a unique singularity in its own context.

Just as it has occurred in many other places before, the passing of a new mental health law in Argentina has proved to be an occasion for deep debate. What was supposed to be good news, as –apparently– we are all in favour of legislation which defends the rights of the patients and guarantees the necessary funds to care for people's mental health in community services, turned out to be an upheaval. To begin with, we all know that setting and time have always been fundamental aspects that affect all our actions. And these elements have played an important role in the passing of this law, as this is a particularly critical political time in Argentina, in which reaching consensus on any subject has proved to be almost impossible, especially due to the example set by the governing party, which works with the binary

logic of good/bad. In this climate, and this being an electoral year (presidential and general elections will take place in October), everything said or written at present unavoidably involves us in such fight, even though we are interested in mental health and not in politics. "A further common mistake is linking inappropriately the reform of mental health care with narrow ideological or party political interests. This tends to lead to instability, as a change of government may reverse the policies of their predecessors. Such fault lines of division or fragmentation may also occur, for example, between service reforms proposed by psychologists and psychiatrists, or even socially and biologically oriented psychiatrists, or between clinicians and service user/ consumer groups. Whatever the particular points of schism, such conflicts weaken the chance that service reforms will be comprehensive, systemic and sustainable, and they also run the risk that policy makers will refuse to adopt proposals that are not fully endorsed by the whole mental health sector."[2]

Consequently, the passing of this law has caused big controversy, especially among professional associations, private mental health services, NGOs which represent users and their families, trade unions which represent health workers, political and economic decision makers, etc.

Historically, the debate of ideas has always been rich in my country. Even when political parties were forbidden, there were discussions taking place among groups which supported psychoanalytic and psychodynamic approaches. In the 50s, 60s and 70s, many supported the anti-psychiatric movement under the leadership of Cooper and Lain, Bassaglia, Castell, etc., as well as the contributions of Tusquet, etc. However, there are many who have learnt that going to extremes leads no where; in fact, tolerance in face of differences and the search for consensus is what enriches any discussion.

Unfortunately, not every one has learnt this lesson. As sketched in the introduction, there are many who still demonize all the developments made in the field of psychiatry. And they also campaign against such developments. They catch the public's attention and they convince legislators, thus spreading the idea that psychiatry may be dangerous. As a consequence, for example, the new law gives similar status to psychiatrists and psychologists when it states that the decision to confine a patient into hospital "should be signed by two professionals, one of whom should be either a psychologist or a psychiatrist". We all know that psychologists play a very important role in mental health care, but the medical training of psychiatrists will surely enable them to make very complex medical decisions. Actually, the decision to confine someone necessarily is a medical intervention, in which there should be a differential diagnosis between an organic illness which affects behaviour (brain trauma, neoplasm, cardiovascular or endocrinological disorders, etc.) and functional mental disorders. And the same occurs when pharmacological treatments become necessary. Medication should be prescribed competently and responsibly in order to avoid as many side affects as possible. Such decisions, I insist, can only be made by a certified physician. Nick Craddock and Bridget Craddock have expressed it this way "Psychiatrists are medically trained. They are the members of a mental health team that have expertise in diagnosis and management of physical illness. They have training in the biological disciplines of physiology, biochemistry, anatomy, pathology and pharmacology. They have training in diagnostics. Given the importance of identifying the key issues as early as possible and setting the patient along the most appropriate therapeutic path, the psychiatrist is the special ist who can undertake/coordinate effectively the initial diagnostic assessment process and make appropriate diagnostic reviews if new information arises. The psychiatrist is uniquely placed to take account of physical illness, both as a contributor to the psychiatric picture (for example when thyroid dysfunction contributes to affective disturbance) or as a comorbid condition (such as recognizing heart disease co-occurring with depression) or as an adverse effect of psychiatric treatment (such as type 2 diabetes associated with treatment by antipsychotic medication). Finally, in addition to the psychiatrist's core medical skills, he/she has training in psychological and social issues. Thus, the psychiatrist is uniquely placed to take the "big picture" overview that includes the biological, psychological and social domains within the assessment."[3] Unfortunately, in a way, this law does not consider interdisciplinary teams as a sum of different knowl-

edge; in fact, it erases the boundaries between professions, thus leading to confusion.

Some other aspects to be mentioned about this law are that no reference is made to out patient services, although they are of utmost importance in everyday practice, and that there is a bureaucratization of hospitalization. Such decision is no longer made professional by a, as a means to achieve the best treatment possible, but by a the judge's, who is expected to know what is best for the patient. Besides, the law creates a new supervising agency, which will supervise the judges' decisions, instead of appointing the Office of Public Prosecutor to perform this task, an office which already exists. Consequently, due to bureaucracy, there is little hope that this office will be created in the near future.

By definition, the passing of a good law is promising, as we expect to improve what we have. However, due to various circumstances, my country has seen laws that promised a lot, but they were never implemented. This necessarily results in high scepticism among the population. In fact, many of the biggest developments in psychiatry in our country were produced by people who had a clear view of what would be better for psychiatric patients, rather than by specific laws. For instance, Mauricio Goldenberg, an outstanding dynamic psychiatrist, managed to carry out many important reforms -such as the creation of psychiatric beds in general hospitals, the creation of outpatient services in the community, the training of psychiatrists by means of a residency training program, which was attended by many colleagues who then promoted mental health community services-without new laws being passed.

There are basic contents in this law which are definitely positive: it defends patients' rights; it promotes interdisciplinary team work; it recommends deinstitutionalization, community services and, if necessary, inpatient services in general hospitals. We all agree on this; however, there are many doubts as regards the way this will be put into practice. For example, closing psychiatric institutions is not enough; it is necessary to build new infrastructure for the treatment of patients, such as half way houses, day care centers and so on. This must necessarily be done before psychiatric facilities are closed, as discharged patients must be well supported under the new circumstances. However, this law does not say anything about the creation of these resources which are vital for social rehabilitation of such patients. Besides, the law says that it guarantees that the necessary funds will provide care in community services, but it does not specify where the money will come from, so it is difficult to believe that the money will be available. In fact, it is important to know that Argentina is made up by twenty-four provinces, each of which has its own constitution, laws, authorities, government etc., which must comply with the national constitution. Consequently, the central government may pass a law and recommend a certain course of action, but it cannot make it obligatory due to the federal nature of our political organization; it is the task of each province to adopt and implement it, and without specific funds it is not likely for the reform to take place.

These problems seem to be the natural consequence of the passing of a law for which no consensus was reached beforehand. Many actors were not involved in the writing of the law –professional associations, for example– so they feel it is difficult to accept a law which seems to be inspired by external realities rather than by local circumstances. All stakeholders should participate in the building of any consensus. Otherwise, there will always be people who will react to defend their own interests.

In most countries psychiatry is also threatened by a shortage of psychiatrists. For example, in Argentina the number of medical students who choose this branch of medicine as their specialty has declined during the past twenty years, while the number of prospective psychologists has soared.

These are some of the reasons why many believe that psychiatry is being discredited. In fact, Mario Maj, President of the World Psychiatry Association, has stated "Indeed, we and our profession are stigmatized in many countries of the world. This is certainly related to our difficulty to convey the new image of psychiatry: the image of an integrative discipline, which deals with a broad range of disorders, including some that are very common in the population, using interventions that are at least as effective as those available to most other branches of medicine. However, it would not be fair to state that psychiatry has just a problem with promoting

more successfully its new image. It has to be acknowledged that our profession also has a problem, in several contexts which vary from one country to another, with matching up to this new image in the reality of clinical practice, research and training."[4] Thus, he places the solution within our reach: we have to show the public what the new psychiatry is, and live up to it. A WPA Task Force appointed to develop a guide on how to combat stigmatization of psychiatry and psychiatrists. "...recommended that national psychiatric societies establish links with other professional associations, with organizations of patients and their relatives and with the media, in order to approach the problems of stigma on a broad front. The Task Force also underlined the role that psychiatrists can play in the prevention of stigmatization of psychiatry, stressing the need to develop a respectful relationship with patients, to strictly observe ethical rules in the practice of psychiatry and to maintain professional competence."[5]

In this scenario, in which there are both internal and external risks for psychiatry, the question we should ask ourselves is: Are we providing patients with what they need? Is there any other way of helping them? The answer to these questions should come from avoiding militant attitudes and the ideologization of reality. We should learn from past lessons –whether they are local or foreign– and, most important of all, focus on the people. In this line, the International Network for Person-centered Medicine (INPCM) has been a pioneer in the building of new bonds among different professions and advocacy groups to improve medical care.* The original initiative was born in 2005, focusing on "the whole person of the patient in context as the center and goal of clinical care and health promotion, at both individual and community levels. This involves the articulation of science and humanism to optimize attention to the ill and positive health aspects of the person. As care is basically a partnership experience, the program involves the integration of all relevant health and social services. Furthermore the program also involves advancing propitious public health policies."[6]

Let us always remember that our main professional interest is basedon in improving our patients' quality of life, which obviously includes their mental health. We have to be as creative as possible to find the best way to do so.

* Members of the International Network for Person-centered Medicine (INPCM)
- World Medical Association (WMA)
- World Organization of Family Doctors (WONCA)
- World Health Organization (WHO)
- International Alliance of Patients' Organizations (IAPO)
- International College of Surgeons
- International Council of Nurses (ICN)
- International Federation of Gynecology and Obstetrics (FIGO)
- International Federation of Social Workers (IFSW)
- International Federation on Aging
- International Pharmaceutical Federation (FIP)
- Council for International Organizations of Medical Sciences (CIOMS)
- Medical Women's International Association,
- World Federation for Mental Health (WFMH)
- World Federation of Neurology (WFN)
- World Association for Sexual Health (WAS)
- World Association for Dynamic Psychiatry (WADP)
- International Federation of Medical Students' Associations (IFMSA)
- World Federation for Medical Education (WFME)
- International Association of Medical Colleges (IAOMC)
- European Association for Communication in Health Care (EACH)
- European Federation of Associations of Families of People with Mental Illness (EUFAMI)
- Ambrosiana University
- University of Buckingham
- University of Geneva
- Hospitals of Geneva (HUG)
- Paul Tournier Association

Εξελίξεις και προοπτικές στην ψυχική υγεία. Υπάρχει προκατάληψη για την ψυχιατρική;

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Η ειδικότητα της Ψυχιατρικής και η διεπιστημονική εργασία που επιτελείται από τους ψυχιάτρους σε σύνδεση με τους υπόλοιπους επιστημονικούς και ανθρωπιστικούς κλάδους, επηρεάζονται από κάποια γεγονότα που έχουν ως αποτέλεσμα τον στιγματισμό τους. Υπάρχουν τόσο εσωτερικοί όσο και εξωτερικοί παράγοντες που επηρεάζουν το επάγγελμα. Ανάμεσα στους εσωτερικούς παράγοντες πρέπει να αναφερθούν τα διαφορετικά κριτήρια που χρησιμοποιούν οι ψυχίατροι για τη διάγνωση των ψυχιατρικών νοσημάτων, καθώς και οι υπάρχουσες διαφορές στη θεραπευτική αντιμετώπισή τους. Επιπλέον, η ψυχιατρική πράξη μπορεί να διαφοροποιείται πολύ ανάλογα με τον βιολογικό, ψυχολογικό, πολιτισμικό ή κοινωνικό προσανατολισμό του ψυχιάτρου που εξετάζει την κάθε περίπτωση. Οι εσωτερικές αναντιστοιχίες πυροδοτούν τους εξωτερικούς κινδύνους που αντιμετωπίζουν τόσο οι ψυχίατροι όσο και η ψυχιατρική: την αμφισβήτηση και την έλλειψη εμπιστοσύνης των ασθενών, τη διείσδυση άλλων κλάδων στον χώρο της Ψυχιατρικής και την αρνητική εικόνα που έχει η κοινή γνώμη για την Ψυχιατρική. Στην Αργεντινή, όπως και σε πολλά άλλα μέρη του κόσμου στο παρελθόν, η ψήφιση του νέου νόμου για την ψυχική υγεία έγινε η αφορμή για σοβαρές συζητήσεις και έντονο προβληματισμό. Η συζήτηση του νόμου δημιούργησε πολλές διχογνωμίες και αντίθετες τοποθετήσεις ανάμεσα στις επαγγελματικές εταιρείες, τον ιδιωτικό τομέα παροχής υπηρεσιών, τις ενώσεις που αντιπροσωπεύουν τους χρήστες και τις οικογένειές τους, τα σωματεία των εργαζομένων στο τομέα της υγείας, τα πολιτικά και οικονομικά κέντρα αποφάσεων και ούτω καθεξής. Στην Αργεντινή ο ιδεολογικός προβληματισμός και οι συζητήσεις ήταν πάντα πλούσια. Ακόμη και την περίοδο της απαγόρευσης των πολιτικών κομμάτων, υπήρχαν συζητήσεις ανάμεσα σε ομάδες που υποστήριζαν τις ψυχαναλυτικές και ψυχοδυναμικές απόψεις. Υπάρχουν πολλοί που δαιμονοποιούν τις εξελίξεις και την πρόοδο της Ψυχιατρικής και πρωτοστατούν εναντίον αυτών των εξελίξεων. Καταφέρνουν να παρασύρουν την κοινή γνώμη και πείθουν τους νομοθέτες διαδίδοντας την άποψη ότι η Ψυχιατρική μπορεί να είναι επικίνδυνη. Ως συνέπεια, ο νέος νόμος τοποθετεί στο ίδιο επίπεδο τους ψυχιάτρους και τους ψυχολόγους όταν αναφέρει πως η απόφαση για νοσηλεία ενός ασθενούς «πρέπει να υπογραφεί από δύο επαγγελματίες, εκ των οποίων ο ένας πρέπει να είναι είτε ψυχίατρος είτε ψυχολόγος». Όλοι γνωρίζουμε ότι οι ψυχολόγοι έχουν έναν πολύ σημαντικό ρόλο στη φροντίδα της ψυχικής υγείας, αλλά μόνο η ιατρική εκπαίδευση των ψυχιάτρων μπορεί να διασφαλίσει τη λήψη σύνθετων ιατρικών αποφάσεων, όπως για παράδειγμα την ανάγκη νοσηλείας ενός ασθενούς στο νοσοκομείο. Άλλες πλευρές αυτού του νόμου που αξίζει να αναφερθούν είναι η απουσία αναφοράς σε εξωνοσοκομειακές υπηρεσίες, παρόλη τη σπουδαιότητα που έχουν στην καθημερινή πρακτική και τη γραφειοκρατία που υπάρχει στη νοσοκομειακή φροντίδα. Αυτές οι αποφάσεις δεν βαραίνουν πλέον τον επαγγελματία στο πλαίσιο της βέλτιστης άσκησης του επαγγέλματός του, αλλά τον δικαστή ο οποίος καλείται να γνωρίζει τι είναι το καλύτερο για τον ασθενή. Παρόλ' αυτά, υπάρχουν και θετικά σημεία: Υπερασπίζεται τα δικαιώματα των ασθενών, προωθεί τη διεπιστημονική ομαδική δουλειά, προτείνει την αποασυλοποίηση, τις κοινοτικές υπηρεσίες και, αν είναι απαραίτητο, τις ενδονοσοκομειακές υπηρεσίες στα Γενικά Νοσοκομεία. Υπάρχουν βέβαια πολλές αμφιβολίες σχετικά με τη δυνατότητα πραγματοποίησης αυτών των συστάσεων. Στις περισσότερες χώρες, η ψυχιατρική απειλείται, εκτός των άλλων και από τη μείωση του αριθμού των ψυχιάτρων. Στην Αργεντινή εκτός των άλλων, παρατηρείται μείωση του αριθμού των φοιτητών της Ιατρικής που επιλέγουν ως ειδικότητα την Ψυχιατρική τα τελευταία χρόνια, ενώ ο προβλεπόμενος αριθμός των ψυχολόγων έχει αυξηθεί. Αυτοί είναι κάποιοι από τους λόγους που αρκετοί πιστεύουν ότι έχουν οδηγήσει στην απα-

ξίωση της ψυχιατρικής. Σύμφωνα με αυτή την τοποθέτηση, κατά την οποία τόσο εσωτερικοί όσο και εξωτερικοί κίνδυνοι απειλούν την Ψυχιατρική, το δικό μας επαγγελματικό ενδιαφέρον οφείλει να είναι προσανατολισμένο στη βελτίωση της ποιότητας ζωής των ασθενών μας, η οποία προφανώς περιλαμβάνει και την ψυχική τους υγεία. Προκειμένου να επιτύχουμε καλύτερα αποτελέσματα, πρέπει να αποφεύγουμε τις πολεμικές συμπεριφορές καθώς και την ιδεολογικοποίηση της πραγματικότητας, και να είμαστε όσο πιο δημιουργικοί γίνεται προκειμένου να επιτύχουμε όσο καλύτερα γίνεται τον στόχο μας.

Λέξεις ευρετηρίου: Ψυχική υγεία, στίγμα, εξελίξεις, προοπτικές

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Special article
Ειδικό άρθρο

Stress and personality

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Stress is an adaptation reaction of living organisms in response to internal or external threats to homeostasis. It is considered as a complex defence mechanism representing the final end point of numerous dynamic and interconnected factors of biological, psychological and social nature. Stress is not a simple, stimulus-response reaction, but the interaction between an individual and the environment, involving subjective perception and assessment of stressors, thus constituting a highly personalized process. Specific inherited characteristics, early experience in life, and particular, learned cognitive predispositions make individuals more or less susceptible to the effects of stressors. Resilience and vulnerability to stressors as well as intensity of stress response are greatly dependable on age, gender, intelligence, and numerous characteristics of personality, such as hardiness, locus of control, self-efficacy, self-esteem, optimism, hostility (component of type A personality) and type D traits (negative affectivity and social inhibition). To understand the relation between personality and stress, it is essential to recognize the impact of individual differences in the following four aspects: (1) choice or avoidance of environments that are associated with specific stressors, challenges or benefits, (2) way of interpreting a stressful situation and evaluating one's own abilities and capacities for proactive behaviour so as to confront or avoid it, (3) intensity of response to a stressor, and (4) coping strategies employed by the individual facing a stressful situation. Studies have recorded considerable consistency in coping strategies employed to confront stressful situations, independently of situational factors and in connection with permanent personality and temperamental traits, such as neuroticism, extraversion, sense of humour, persistence, fatalism, conscientiousness, and openness to experience. Positive affect has been associated with positive reappraisal (reframing) of stressful situations, goal-directed problem-focused coping, using spiritual or religious beliefs to seek comfort, and infusion of meaning into the ordinary events of daily life in order to gain a psychological time-out from distress. Characteristics of a resilient personality are: ability to cope in stressful situations, continuing engagement in activities, flexibility to unexpected changes in life, ability to seek social support, perceiving stress as a challenge – a chance for growth and development rather than a threat to life, taking care of one's body, living in harmony with nature, optimism and sense of humour, work and love, developing spiritualism and seeking true sense. The tolerance threshold is individual. However, even persons with mature and integrated personalities exposed to prolonged stress may experience failure of their adaptive capacities and psychological or somatic decompensation. During the last years, Life Skills Education has become the focus of particular attention. Educational programs aim at developing the capacities for critical thinking, analyzing and problem-solving, building of self-confidence, confronting various negative pressures imposed by the environment, improving self-assessment, developing communication and social adjustment skills, and gaining control over stressors and one's own affective and behavioral response. Finally, special programs for individual vulnerable population groups (teenagers, elderly persons, patients with AIDS, addictions, etc.) have been introduced so as to strengthen their ability to handle specific stressful situations.

Key words: Stress, personality, coping styles, resilience, vulnerability

Introduction

Living organisms survive by maintaining the complex, dynamic and harmonious balance or homeostasis that has continuingly been challenged, i.e. threatened by internal or external deterioration factors. Adapting to changes has been enabled by numerous and various defence mechanisms, confronting and recreating the disturbed balance.[1] Accordingly, stress is defined as the state of disharmony or a threat to homeostasis. The adaptation response may be either specific or general and non-specific in terms of a stress reaction. From today's perspective, the comprehension of stress exclusively as the reaction of organism to certain external stress stimuli may be characterized as reductionistic.[2] Lazarus and Folkman expanded the stress theory, pointing out that an individual and environment are not independent entities, but instead, interconnected components.[3] One of the major characteristics of such relationship is that an individual appraises (either reasonably or not) that new circumstances, provoked by psychosocial stressors, may exceed his/her abilities and capacities to successfully confront them. Hence, it is not only the matter of simple reaction to stressor impact. The transactional model singles out the importance of cognitive processes and individual differences, out of other stress components, when it comes to the appraisal of events in external environment.[3] Significant individual differences in reactions have been identified, even to the same stressors of the same intensity. Lazarus rightfully pointed out that the reaction to stress is a highly personalized process, i.e. the process that vastly depends on characteristics of a person.[4,5]

Personality is a system defined by features and dynamic processes that jointly affect the psychological functioning and behaviour of an individual.[6] It is a unique, integrated motivation and cognitive "universe", dynamic centre of consciousness, emotions, reasoning and actions, organized as wholes that significantly differ from other wholes, depending on social and natural environment.[7]

Personality represents one of the significant links for understanding stress, while the attempts to connect the types of personalities and illnesses originate back from Hippocrates who said that it's far more important to know what person has a disease than what disease the person has. Since the time of Hippocrates, the psychological types of personalities or "temperaments" attracted attention of scientists in the effort to explain differences between individual responses and diseases. The fact that the link between emotions, personality and diseases was written about as early as two thousand years ago, indicates that to a certain point, they are true, but certainly, the theoretical framework is quite flexible and adaptable to different observations and ways of thinking. During further development of medicine, such approach has been neglected, until nineties of the former century, though it has been continuously appreciated in some traditional medical systems (such as the Ayurvedic medicine).[4,8]

Resilient *vs* vulnerable personality

Stressful reaction is rather complex and represents the termination of dynamic activities and interactions of numerous factors of biological, psychological and social nature. The stress is not a simple stimulus-response reaction, but rather an interaction between an individual and environment, involving subjective perception and appraisal of stressors, hence representing a highly personalized process.[4]

Capacities enabling a person to overcome difficulties and productively contributing to one's development deserve special attention of personality psychology. It is quite certain that specific inherited characteristics, early experience in life and particular, learned cognitive predispositions make individuals more or less susceptible to effects of stressors. However, as Bandura[9] and Kagan[10] pointed out, individual ways of coping with stressful situations are equally important. The resilience model involves successful adjustment or homeostasis, and this has been demonstrated by the Scale of Defensive Functions, according to DSM-IV,[11] classifying the mechanisms of coping according to their adaptability values.

Resiliency as well as vulnerability to stressors and intensity of response to stress is greatly dependable on numerous characteristics of personality and age. Children and young persons are more susceptible to the impact of almost any stressor. Where a traumatic stress is experienced during a formative period, it

may have adverse effect on the future personality development. Some researchers have discovered that as many as 60% of persons diagnosed with borderline personality disorders[12] had been exposed to abuse during their childhood. In contrast to that, many persons have productive, well adjusted lives in spite of difficult experiences at the beginning of their development. Relatively positive outcomes in lives of the Second World War orphans that had later been adopted by middle class families, support the trends of self-expression in the psychological development.[13,14] Similarly, the research made in the field of developmental psychopathology points to the resiliency displayed by individuals.[15,16]

Elderly persons are more resilient to psychosocial stressors. Nevertheless, the reduction of physical abilities as well as emotional adaptability to changes makes the elderly persons feel that they are becoming less able to control their destiny. When it comes to biological stressors, elderly persons often display increased vulnerability, which may be explained by a more frequent presence of disorders and illnesses among this population.[4]

Gender differences in response to stress are predisposed by biological factors, status differences, roles and expectations from genders in certain environments.[17] The intelligence also affects resilience to stress. More intelligent persons are more successful and objective with assessing a stressful situation and their own ability to confront it. However, there are many exceptions to this rule. Affective response and capacity of controlling own affective behaviour in many situations are essential.[4] Therefore, resiliency i.e. vulnerability to stress, as well as ability to confront and cope with stress, depend on cognitive and affective characteristics of a person, including the person's psychological organization and dominant defence mechanisms exercised by persons in stressful situations.[17,18]

Most of the studies that dealt with relation between personality and stress have not focused on wider categories of the personality dimensions, but rather on lower-order traits, such as hardiness, optimism, locus of control, assessment of own efficiency etc.[19] A hypothesis has been made, based on the clinical experience and research, that some types of personalities are generally displaying more hardiness in stressful situations, meaning that they are more resilient, and/or susceptible to diseases. Suzanne Kobasa[20,21] defined a hardy personality having three crucial characteristics: (a) ability to control oneself and stressful events occurring in course of one's life; (b) continuing involvement in activities, consistently following specific life path and (c) flexibility to adjust to unexpected changes in life, accepted as challenges or continuity interruptions and a chance for personal growth and development, rather than a threat to life.[4]

One of the components of personality hardiness, locus of control, plays a significant role as a mediator between stress, health and well-being. The research has shown that a high level of self-efficacy and self-esteem act protectively. Self-efficacy and self-esteem are particularly significant in overcoming distress caused by negative response of environment and/or one's failure. Moreover, it has been shown that another significant factor besides the level of self-esteem is the level of stability. High, but instable self-esteem is being connected with a higher level of hostility and rage.[22] Kernis believed that a high but unstable self-esteem represented one of the forms of a "fragile self-esteem".[22] Optimism is different from former control-based concepts, since it does not necessarily imply that the flow of events is influenced by the action of an individual. Such characteristic of personality may rather be said to involve one's belief that events would in any case take a favourable course, which is basically connected with the attitude that the world is benevolent. It has been shown that optimism contributes to the stress appraisal, coping strategy and general well-being and health.[23]

Hostility represents a "toxic" component of Type A behaviour that has been confirmed to be connected to neurendocrine, cardiovascular and emotional response to interpersonal stress. The hostility concept comprises three components: (a) cognitive (hostile beliefs and attitude towards others – cynicism, mistrust etc.), (b) emotional (rage) and (c) behavioural (physical and verbal attacks and threats). Expression of rage and hostility attracts special attention of researchers, taking into account that it clearly proved its connection with coronary diseases.[23] However, the results of research about the connection between Type A personality and coronary diseases are rather inconsistent. Quite recently, Johan Denollet and associates[24] from Tilburg University, Netherlands, noticed

the connection between the specific type of personality and coronary diseases. The new concept of distress-prone personality, or the so called Type D, was thus introduced.[25] These persons are inclined to experiencing intensive negative emotions, without displaying them, for the fear of the reaction of the environment. The proposed taxonomy relies on two general and stable dimensions, marked as Negative Affectivity (NA) and Social Inhibition (SI).[24] We have also shown a decreased cardio-vascular reactivity of persons belonging to Type D personality, during the mental stress test (anger recall task), that at least partly may be explained by exhausting adaptive capacities due to higher exposure to chronic distress.[26]

Potential mechanisms of personality influence on stress

People are not inert beings predisposed to have the same reactions to specific stressful stimuli. Key factors for understanding the relationship between personality and stress are individually specific potentials reflected in difference in choice, way of interpreting, reacting and influencing the situations they come across.[27] Potentials are present not only in persons, but the environment as well. The environment is not imposed to a person; a person is the one who chooses it. People choose environments that confirm their personal and professional lives. Even when a person chooses the environment, a number of his/her potentials and abilities will only remain latent, if there are no proactive choices made. One of the stable manifestations of individual differences is actually reflected in situations that a person chooses or avoids. Certain persons protect themselves from stress by avoiding such challenges, but by doing so they also forsake their opportunity to experience success, personal growth and development. Competitive persons seek jobs with equally competitive, and thereby highly stressful environment (displaying poor cohesion, low level of co-operation, mistrust), but the success in work brings along a variety of benefits.[23]

The way in which a person evaluates own abilities and capacities for proactive behaviour and prospective to succeed when confronted with a stressful situation, is equally essential. This is another mechanism describing the relationship between personality and stress. The evaluation may turn out to be realistic or non-realistic, in terms of overestimating or underestimating one's own abilities and capacities to confront stressors or to avoid them. The first are more prone to paying attention to current and potentially positive aspects of a stressful situation, by redefining and interpreting it, such as by conceiving it as part of an everyday life, rather than a tragedy. Others, however, are prone to perceive only negative aspects of stressful situations and even exaggerate them. Thus, for example, hostile persons are more prone to focus on "signals" of hostility in others and seek for their confirmation in unclear situations, while persons who score high on neuroticism experience most of events as problematic, and thereby stressful as well. High neuroticism also comes along with extreme reactivity to negative events.[28] Different intensity of response to stressful situations being the third mechanism of relation between personality and stress has also been displayed by other dimensions. Hence, extraverts experience stronger reaction to positive events, while hostile persons display the highest reactivity to social stressors. The fourth mechanism is the way in which personality confronts stress.

Personality and ways to cope with stress reactions

Personality characteristics and coping strategies are related to differences in stress situation appraisal.[29] In their comprehensive, seven-year Baltimore Longitudinal Study, McCrea and associates[30] examined the determinants of stress coping and importance of personality, relying on the Five-Factor Model. It has been discovered that aside from situational factors, formerly believed to constitute almost exclusive factors for choosing the way to cope with stress, there is consistency in coping with stress that is connected with permanent personality traits. Thus, faith and fatalism used to be linked with loss, and persistence and sense of humour with challenges.[30]

Coping consistency and connection with some personality traits have also been identified by the study conducted on adolescent population, concluding that the choice of strategy of confronting stress is largely consistent, regardless of the nature of problems[31] and that it depends on temperament.[32] Smith

and associates[33] pointed to the fact that *neuroticism* was less frequently connected with focused coping and seeking social support, and more frequently with attempts to use imagination and avoidance. Endler and Parker[34] reported high correlation between neuroticism and emotion-oriented coping. These results are not surprising, considering that negative emotions are the part of stress, while neuroticism is sometimes defined as inclination towards negative emotions.[35] Any attempt to comprehend the situational determinants of stress and coping has to take into account the neuroticism as well.

The role of extraversion is less clear. The unity of extraversion and coping strategy such as humour, a need to discuss feelings and seeking social support, has been confirmed.[36] Gallagher[37] stated that persons scoring high on extraversion scale perceived academic stressors as challenges, rather than threats. Generally, extraversion is connected with proactive, social and optimistic ways of coping with stress.

Co-operativeness is connected with stoic and submissive attitude when encountering stressors. Considering that the dimension *conscientiousness* involves traits such as persistency, self-discipline and planning, it may be expected that it is associated with efficient coping. One of the several studies tackling this issue, has shown strong correlation (r=0.44) between the *conscientiousness* and problem solving, as one way to cope with stress.[38] In their new study, Spirrison and associates[39] came up with the new correlation of 0.62 both between the dimension of conscientiousness and NEO-PI-R inventory and the behavioural coping scale from the Constructive Thinking Inventory by Epstein and Meier.[40]

The dimension *openness to experience* is the predictor of positive coping, involving connecting, coping with problems – the transcendence, etc.[41] Trusting others, as one of the components of agreeableness dimension, is positively correlated with seeking social support.[42]

Folkman[43] found that the coping affected health through its mediating variables (such as mood). She raised the question whether coping affected mood or mood affected coping, and named studies which suggested that this was a two-direction possibility. However, the majority of studies on coping dealt with coping→mood, rather than mood→coping relationship. The field that had often been neglected in studying the relation between coping and health, refers to the ability of proper functioning when facing extreme difficulties, in relation to which Folkman[43] referred to the role of positive affect. After having analyzed the results of several studies examining the connection between positive and negative affects and health, Folkman asserted that positive situations, whether being the outcome of positive events or positive affects, had three important functions when coping with chronic and severe stress. Positive emotions help motivate people to initiate coping, to proceed with their lives when things become tough and ameliorate distress.

The research of Folkman and associates has identified four mechanisms of coping, relying on significance/meaning that help explain the role of positive affect: (a) positive reappraisal, refers to cognitive reframing of what has happened or what could have happened; (b) goal-directed problem-focused coping, which includes knowing when to abandon goals that are no longer tenable and replace them with new goals that are both tenable and meaningful; (c) using spiritual or religious beliefs to seek comfort; and (d) infusion of meaning into the ordinary events of daily life in order to gain a psychological time-out from distress.[43]

In contrast to that, Type A personality (coronary-prone personality) epitomises the style of coping focused on negative emotions.[44] Concurrently, Type A personality is characterized with avoidant coping style.[45,46] Also, Scheier and Carver[47] have shown that optimists use problem-focused strategies more often than pessimists.

Conclusion

Lecic-Tosevski and associates[17] named some of the factors describing a resilient personality. The list represents the synthesis of standpoints presented in the literature, including thoughts of the authors: ability to cope in stressful situations, continuing engagement in activities, flexibility to unexpected changes in life, ability to seek social support, perceiving stress as a challenge – a chance for growth and development rather than a threat to life, taking care of one's body, living in harmony with nature, optimism and sense of humour, work and love, developing spiritualism and seeking true sense.[17,48–50]

It is easy to conclude that this in fact is the description of an integrated, mature personality. However, it should be pointed out that the level of tolerance differs from person to person, and that even the most mature personalities exposed to prolonged stress may experience breakdown of their adaptive capacities and decompensation, either psychological or somatic one.[50]

During the last years, Life Skills Education has become the focus of attention. These skills may prevent or ameliorate effects of psychosocial consequences of stress. Educational programs are particularly being devoted to developing the capacities for critical thinking, analyzing and problem-solving including decision making and their implementing. Further crucial elements of such education are building of self-confidence and confronting various negative pressures imposed by the environment, improving self-assessment, developing communication skills and skills of social adjustment. When it comes to the stressful situation, the focus is on having the education that would enable an individual to be as efficient as possible in gaining control over stressors (whenever possible) and own affective response and behaviour. Special programs for individual groups of population (teenagers, elderly persons, the wounded, persons living in collective dwellings etc.) have been introduced, in addition to general education programs developing life skills. Such programs have been developed to handle specific stressful situations they have been exposed to. Furthermore, there are special programs developed for persons under high risk from sexually transmitted diseases (such as AIDS and other), addiction disorders, and various other categories of vulnerable population.[4]

Stress και προσωπικότητα

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Το στρες είναι αντίδραση προσαρμογής των ζώντων οργανισμών ως απάντηση σε εσωτερικές ή εξωτερικές απειλές της ομοιόστασης. Θεωρείται σύνθετος αμυντικός μηχανισμός όπου συντείνουν πολυάριθμοι δυναμικοί και αλληλοδιαπλεκόμενοι βιοψυχοκοινωνικοί παράγοντες. Το στρες δεν είναι απλώς αντίδραση ερεθίσματος-απάντησης αλλά αλληλεπίδραση του ατόμου με το περιβάλλον που ενέχει υποκειμενική αντίληψη-εκτίμηση των ψυχοπιεστικών παραγόντων, αποτελώντας, έτσι, μια ιδιαίτερα εξατομικευμένη διεργασία. Κληρονομούμενα χαρακτηριστικά, πρώιμες εμπειρίες ζωής και μαθημένες νοητικές διεργασίες καθιστούν τα άτομα περισσότερο ή λιγότερο ευάλωτα στην επίδραση των ψυχοπιεστικών γεγονότων. Η ανθεκτικότητα και η ευαλωτότητα στους ψυχοπιεστικούς παράγοντες καθώς και η ένταση της αντίδρασης στρες εξαρτώνται σε μεγάλο βαθμό από την ηλικία, το φύλο, τη νοημοσύνη και πολυάριθμα χαρακτηριστικά προσωπικότητας, όπως η αντοχή, η έδρα του ελέγχου, η αυτοεπάρκεια, η αυτοεκτίμηση, η αισιοδοξία, η εχθρικότητα (συστατικό της προσωπικότητας τύπου Α) και στοιχεία προσωπικότητας τύπου D (αρνητικό συναίσθημα και κοινωνική αναστολή). Για την κατανόηση της σχέσης μεταξύ προσωπικότητας και στρες, είναι ουσιώδες να αναγνωρισθεί η σημασία ατομικών διαφορών στα ακόλουθα 4 πεδία: (1) επιλογή ή αποφυγή περιβαλλόντων που σχετίζονται με ιδιαίτερους ψυχοπιεστικούς παράγοντες, προκλήσεις ή οφέλη, (2) τρόπος ερμηνείας μιας ψυχοπιεστικής συνθήκης και εκτίμηση των ικανοτήτων του ατόμου για ενεργό δράση ώστε να την αντιμετωπίσει ή να την αποφύγει, (3) ένταση της απάντησης σε έναν ψυχοπιεστικό παράγοντα, και (4) στρατηγικές που χρησιμοποιεί το άτομο για την αντιμετώπιση μιας ψυχοπιεστικής συνθήκης. Μελέτες έχουν καταγράψει σημαντική συνέπεια στις στρατηγικές που χρησιμοποιούνται για την αντιμετώπιση ψυχοπιεστικών συνθηκών, ανεξάρτητα από περιστασιακούς παράγοντες και

σε σχέση με μόνιμα χαρακτηριστικά της προσωπικότητας ή της ιδιοσυγκρασίας, όπως ο νευρωτισμός, η εξωστρέφεια, η αίσθηση του χιούμορ, η επιμονή, η μοιρολατρία, η ευσυνειδησία και η αναζήτηση εμπειριών. Το θετικό συναίσθημα έχει σχετισθεί με θετική επανεκτίμηση (αναπλαισίωση) των ψυχοπιεστικών συνθηκών, στοχο-κατευθυνόμενη εστιασμένη στο πρόβλημα αντιμετώπιση, χρήση πνευματικών ή θρησκευτικών πεποιθήσεων σε αναζήτηση ανακούφισης, και νοηματοδότηση απλών γεγονότων της καθημερινής ζωής με στόχο τη μείωση του άγχους. Χαρακτηριστικά μιας ανθεκτικής προσωπικότητας είναι: η ικανότητα αντιμετώπισης ψυχοπιεστικών συνθηκών, η συνέχιση της εμπλοκής σε δραστηριότητες, η ευελιξία σε απρόσμενες μεταβολές στη ζωή, η ικανότητα αναζήτησης κοινωνικής στήριξης, η θεώρηση του στρες ως πρόκλησης- ευκαιρίας για ανάπτυξη παρά ως απειλής στη ζωή, η αυτοφροντίδα, η εναρμόνιση με τη φύση, η αισιοδοξία και η αίσθηση του χιούμορ, η εργασία και η αγάπη, η ανάπτυξη πνευματικότητας και η αναζήτηση αληθινού νοήματος. Ο ουδός ανοχής εξατομικεύεται. Ωστόσο, ακόμη και άτομα με ώριμες και ολοκληρωμένες προσωπικότητες μπορεί να εμφανίσουν κατάρρευση των προσαρμοστικών τους ικανοτήτων και ψυχολογική ή σωματική απορρύθμιση μετά από έκθεση σε παρατεταμένο στρες. Τα τελευταία χρόνια, η Εκπαίδευση στις Δεξιότητες Ζωής αποτελεί αντικείμενο ιδιαίτερης προσοχής. Τα εκπαιδευτικά προγράμματα στοχεύουν στην ανάπτυξη των ικανοτήτων κριτικής σκέψης, ανάλυσης και επίλυσης προβλημάτων, στην οικοδόμηση της εμπιστοσύνης στον εαυτό, στην αντιμετώπιση των ποικίλων αρνητικών πιέσεων από το περιβάλλον, στη βελτίωση της αυτοαξιολόγησης, στην ανάπτυξη δεξιοτήτων επικοινωνίας και κοινωνικής προσαρμογής, και στην απόκτηση ελέγχου επί των ψυχοπιεστικών παραγόντων και επί της συναισθηματικής και συμπεριφορικής ανταπόκρισης του ατόμου. Τέλος, έχουν αναπτυχθεί ειδικά προγράμματα για ευάλωτες πληθυσμιακές ομάδες (εφήβους, ηλικιωμένους, ασθενείς με AIDS, εξαρτήσεις, κ.λπ.) με στόχο την ενίσχυση της ικανότητας διαχείρισης ειδικών ψυχοπιεστικών συνθηκών.

Λέξεις ευρετηρίου: Στρες, προσωπικότητα, στρατηγικές αντιμετώπισης, ανθεκτικότητα, ευαλωτότητα

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Special article
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Problems in determining efficacy and effectiveness of antidepressants

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Antidepressants play the major role in treating depressive patients not only due to the fact that they have to undergo the most rigorous proof of efficacy but also because they are easy to apply in the everyday clinical practice. Nearly all psychiatrists and general practitioners treating depressive patients agree about the relevance of antidepressants in the treatment of depressive patients. However, a number of meta-analytic studies recently challenged this belief and it has been put up for discussion to psychiatry/clinical psychopharmacology whether the efficacy of antidepressants is clinically relevant. Despite that all medication were judged to have sufficient data to receive approval from the FDA and the EMA and other agencies worldwide, some authors went further and questioned the effectiveness of antidepressants. They even proposed that "alternative" therapies of unproven efficacy or of proven negative efficacy should be preferred to medication. These authors do not take into consideration that for methodological reasons it is not acceptable to deduce too extensive conclusions. Some assumptions they rely on, like the suggestion of NICE, which regards a mean placebo-verum difference of 3 HAM-D points as clinically relevant, is downright arbitrary on statistical grounds, and not supported by empirical findings or by expert opinion. It seems that the difference in change in HAM-D score between the active drug and placebo is somewhere between 2 and 3, with maybe some agents performing a little better than others. It is uncertain whether initial severity determines response; different interpretations exist. However, much more important for the evaluation of the clinical relevance is the result of the responder/remitter analysis, which compares the relative frequency of these categories between the placebo and verum groups. This approach results in a number needed to treat (NNT) of 5–7. In Evidence Based Medicine such a NNT is traditionally regarded as a sign of moderate to strong efficacy and corresponds to the referring values of many therapies, which e.g. are standard therapies in internal medicine. However, from many meta-analyses it is clear that when concepts of evidence-based medicine and health economy are applied, which are far away from clinical thinking, problems occur and results are very difficult to interpret in clinical terms.

Key words: depression, antidepressants, efficacy, effectiveness, tolerability

Introduction

Although pragmatic and focussed strategies of psychotherapy, such as e.g. cognitive behaviour therapy (CBT), have recently gained importance in the treatment of major depressive disorder, antidepressants still play the major role in treating depressive patients.[1–3] This is not only due to the fact that they have to undergo the most rigorous proof of efficacy e.g. in double-blind placebo controlled group studies, before they are licensed by the drug authorities, but also because they are easy to apply in the everyday clinical practice.[4,5] However, like all other antidepressive treatment strategies, the efficacy is limited to a certain degree and in many cases only sequential or comedication approaches lead to sufficient therapeutic results. Although nearly all psychiatrists and general practitioners treating depressive patients agree about the relevance of antidepressants in the treatment of depressive patients, it has recently been put up for discussion to psychiatry/clinical psychopharmacology whether the efficacy of antidepressants is clinically relevant. Others went further and questioned the effectiveness of antidepressants. This is accompanied by a discussion about whether all antidepressants are similar in their clinical efficacy and effectiveness. These three important questions will be discussed in the following, taking study results and methodological issues into consideration. This paper does not claim to be a systematic review but focuses only on some selected issues and refers to the most relevant publications in this context.

Is the efficacy of antidepressants clinically relevant?

At a first glance this question will seem astonishing to most clinicians, since their clinical experience[6] reassures them every day of the clinically relevant efficacy of antidepressants. However, in times of evidence-based medicine and pharmacoeconomics, clinicians have to adapt to a situation in which such common grounds are investigated predominantly by people from outside their own professional community – for example, by evidence-based medicine (EBM) researchers or health economists. These might reach different conclusions because they take into consideration only study results without integrating them into clinical experiences.

The meta-analysis published by Kirsch[7] attracted much attention in this respect, even in the lay press, especially with the provocative conclusion that the efficacy of antidepressants cannot be judged as "clinically relevant". Although the numerical results were not much different from other respective meta-analyses,[8–12] this meta-analysis attracted much more public interest which is per se an interesting phenomenon. Kirsch et al[7] were so far the only group questioning the clinically relevant efficacy of antidepressants and recommending instead alternative approaches of unproven efficacy or proven non-efficacy as a conclusion of their study, although they did not study this subject in their investigation. The paper by Kirsch et al[7] has apparently motivated other authors to go in the same direction, questioning the efficacy of antidepressants. Fournier et al[13] –in this case only based on a meta-analysis of 6 placebo-controlled AD trials, from which the authors were able to collect the original data sets for the individual patients– pointed out that only the very severely affected patients showed a "clinically relevant efficacy".

The meta-analysis by Kirsch et al[7] involving predominantly data on SSRIs, found a mean between the pre-post differences score of the placebo groups and the verum groups of 1.8 HAM-D points, which, although small, is of course statistically highly significant due to its huge sample size. This numerical result was heavily criticized by two recent re-analyses of the data set, demonstrating methodological pitfalls of the Kirsch meta-analysis. Based on these two re-analyses, the correct mean placebo-verum difference amounts to 2.18 or even 2.68, depending on the weighting method used[14] or, even when using, instead of the fixed-effects analysis the more adequately weighted random-effects model, to 2.80.[15] In the context of these reanalyses it was also underlined that for some individual antidepressants the mean placebo-verum difference is even slightly above 3.0, e.g. for venlafaxine and paroxetine,[14] thus reaching the threshold which was seen by Kirsch, following an arbitrary criterion of 3 for clinically relevant efficacy. In addition, Kirsch et al reported that the increase in the efficacy signal in severely depressed patients compared to mildly and moderately depressed patients might be more due to a reduced placebo response in severe depression rather than to an increase in the active drug response. However, these authors failed to interpret this observation

correctly and they stick to the difference between arms. A more appropriate interpretation could be that the active drug is shown to be equally effective in mild and severe depression while the response to the placebo arm seems to be restricted to the milder cases. Taking into consideration also that these observations come from trials with a duration of only a few weeks, it is obvious that the response in the placebo group is unreliable and reflects a combination of methodological problems and the natural course and fluctuation of depression.[14,15]

In interpreting such mean score differences it has to be stated that the mean of the pre-post differences of the placebo groups and the verum groups only give a global estimation of efficacy under the artificial conditions of placebo-controlled trials, in which due to the principal characteristics of the design, the verum response is underestimated and the placebo response is overvalued.[4,16] One cannot conclude very much from this for everyday clinical practice, especially not on the efficacy for special patient subgroups or even for individual patients. Thus, the results obtained in such RCTs should be used more as a methodologically sophisticated proof of concept in a selected group of patients (high internal validity, low external validity) than as an indicator for the size of efficacy/effectiveness under real-world conditions.[17]

The mean of the pre-post differences of the placebo groups and the verum groups only gives a global estimation of efficacy. The placebo *vs* active drug difference in efficacy in different subgroups can be considerably higher[18] due to the high variance for different patient groups.[9,19] This is fairly mentioned by Kirsch et al[7] –supported by Fournier et al 2010–, who found the highest differential effect in severe depression at a placebo-verum mean difference of 4 HAM-D points. The traditional point of view which regarded "endogenous depression/melancholia" as the indication for treatment with antidepressants –tricyclic antidepressants (TCAs) at that time– fit this data analysis well: strong verum efficacy and a low placebo response.[20] The broader ICD-10 category "depressive episode" and similarly the DSM-IV-TR category "major depression" may have caused a softening of the strength of diagnosis and inflation of the indication for AD treatment, and consequently possibly also a thinning-out of the efficacy of antidepressants, due to the higher placebo-response in mild/moderate severity degrees of depression.[2,21,22] It should be emphasized from a clinical perspective that the effectiveness of antidepressants in clinical practice is normally optimised by sequential and combined therapy approaches.[1,23–27]

For methodological reasons it is not acceptable to deduce too extensive conclusions from only one meta-analysis[17] on general placebo-verum differences regarding the clinical relevance the way Kirsch et al[7] do. It should also be understood that different meta-analyses on the same database can come to different results due to different methodologies applied. The meta-analytic approach is also not per se neutral or unbiased as many people might believe and meta-analysts often pretend, as demonstrated by the meta-analytic reanalysis of the dataset of the Kirsch meta-analysis (see above). Depending on the methods applied one can reach more negative or more positive results which make meta-analyses sensitive to any kind of bias.

The principal view of Kirsch et al[7] that a statistically significant mean score difference between placebo and verum group does not automatically result in a clinically relevant efficacy can be principally accepted. To assess the clinical relevance of the differences, Kirsch et al referred to a suggestion of NICE[28] which regards a mean placebo-verum difference of 3 HAM-D points as clinically relevant. Based on this and on the findings of his meta-analysis, Kirsch et al[7] generally deny the clinical relevance of the observed efficacy of SSRIs, except in severe depression. This can be countered by the fact that the cited NICE criterion is downright arbitrary on statistical grounds, but not supported by empirical findings nor by expert opinion.[29] As a contra-argument it should be pointed out that all antidepressants, mostly SSRIs, included in the meta-analysis were approved, among others, by the EMEA and the FDA and their efficacy was therefore obviously considered clinically relevant by the drug authorities.[30]

This leads to the question of whether there is a generally accepted criterion for the clinical relevance of antidepressive effects. This is apparently not the case: there are only different approaches to evaluate this.[31] For the drug approval authorities, apart from a consistent replication of positive study results, the mean of the placebo-verum pre-post score differences of approved antidepressants is definitely of importance, ranging at about 2.0 HAM-D points and reaching statistical significance.[8,10]

Such a mean score placebo-verum difference is therefore to be considered as clinically relevant. However, much more important for the evaluation of the clinical relevance is the result of the responder/remitter analysis,[32] which compares the relative frequency of these categories between the placebo and verum groups. This approach is demanded by health regulatory authorities, like EMA, as an addition to the mean score analyses by drug approval authorities, to determine the clinical benefit of the therapy with an antidepressant. Considering the responder analysis, which Kirsch et al have unfortunately not taken into account in their meta-analytical examination, and counting the patients whose depression values have been reduced by at least 50% of the baseline values, placebo-verum differences ranging at 15–20% are the average result.[33–35] A placebo-verum difference of 15–20% amounts to a number needed to treat (NNT) of 5–7. In EBM such a NNT is traditionally regarded as a sign of moderate to strong efficacy and corresponds to the referring values of many therapies, which e.g. are standard therapies in internal medicine. This consideration equally proves the clinical relevance of SSRIs and antidepressants in general respectively.

Kirsch et al[7] in their critical argumentation considered only short-term studies (up to 8 weeks). If the results of placebo-controlled studies regarding a maintenance therapy with antidepressants (maintenance of the response for 6–12 months after the acute therapy) are considered in the argumentation as well, the conclusion regarding the clinical relevance of antidepressants is even strengthened. Geddes et al[36] in their meta-analysis of 31 randomised, double-blind, placebo-controlled studies found a highly significant efficacy of continuation therapy with relapse rates of 41% under placebo versus 18% under verum. Thus, the placebo-verum difference amounts to 23%, which means a NNT of 4–5.

Kirsch, in his argumentation, seems to advise that a placebo would do as well as an antidepressant. However, it should be understood that the administration of a placebo, justified under double-blind study conditions, cannot for ethical and practical reasons be transferred to everyday clinical practice: If we were to say to the patient, "we will now offer you a placebo", the placebo would already lose its "magic" effect and with this the efficacy.[37]

However, for all these reasons the argumentation of Kirsch et al is misleading and should be rejected.[29] What we need to be aware of just on the basis of the recent meta-analyses is the fact that the mean of the pre-post score differences of the placebo and the verum group amounts to only about 2 HAM-D points RCTs (mostly PIII studies). By interpreting this value it should be taken into consideration that the study conditions in phase-III studies are highly artificial and vulnerable to bias and could possibly underestimate the actual therapy effect of the antidepressant due to the blinding.[4,16]

In everyday clinical practice the efficacy of antidepressants can be regarded as much more pronounced than in placebo-controlled RCTs, especially in the case of patients who have not been pre-treated and are not partial non-responders.[37–40]

Do antidepressants demonstrate sufficient effectiveness?

The concept of effectiveness is difficult to define. It tries to cover the aspect of "real world" performance of a treatment opposite to the results in selected study populations, especially Phase III study populations.[41,42] Apart from the fact that the STAR-D results[43] were interpreted in the sense of effectiveness of antidepressants[44] the concept of effectiveness was so far primarily and predominantly used in clinical psychopharmacology in the field of schizophrenia treatment. There the concept led to several difficulties, when problematic effectiveness measures such as non-discontinuation were used.[45] It can be generally questioned whether "non discontinuation" really reflects only efficacy and tolerability aspects or whether also other parameters beyond drug effects are involved, e.g. the confidence in the therapeutic concept. For example, therapeutic concepts like psychotherapy, herbal drug therapy, etc. might be more acceptable to certain subgroups of patients who highly appreciate these kinds of treatment, although these treatments may have a lower efficacy. Different aspects of tolerability can have different effects on discontinuation, depending on the specific tolerability problems and on the time patterns of side effects. For example, frequent subjectively disturbing side effects (e.g. dry mouth) can have a much higher impact on discontinuation than less frequent but medically more relevant side effects (e.g. metabolic syndromes).

Barbui and co-workers[46] applied the concept of effectiveness to question the relevance of antidepressants in the treatment of depression, using the meta-analyses of placebo-controlled paroxetine studies. They calculated the proportion of patients who left a study earlier for any reasons (drop outs) as the primary outcome measure, because it represents in their view a hard measure of treatment effectiveness and acceptability (or to be more precise than these authors: as a measure of treatment non-effectiveness). They included in the meta-analysis 29 published and 11 unpublished clinical trials, with a total of 3704 patients who received paroxetine and 2687 who received placebo. There was no difference between paroxetine and placebo in terms of the proportion of patients who left the study early for any reason [random effect relative risk (RR) 0.99, 99% confidence interval (CI) 0.88–1.11]. Paroxetine was more effective than placebo, with fewer patients who did not experience improvement in symptoms of at least 50% (random effect RR 0.83, 99% CI 0.77–0.90). Significantly more patients in the paroxetine group than in the placebo group left their respective studies because of side effects (random effect RR 1.77, 95% CI 1.44–2.18) or experienced suicidal tendencies (odds ratio 2.55, 95% CI 1.17–5.54). Based on these results they came to the conclusion that among adults with moderate to severe major depression in the clinical trials reviewed, paroxetine was not superior to placebo in terms of overall treatment effectiveness and acceptability, but on efficacy.

This conclusion, primarily putting efficacy secondary to non-discontinuation as an effectiveness parameter will be seen by most clinical psychiatrists. It clearly indicates that if concepts of evidence-based medicine and health economy are applied, which are far away from clinical thinking, problems occur: Here we encounter the situation that an antidepressant, which in the Kirsch meta-analysis[7] came out as a superior one in terms of efficacy, although it included the non-published studies in the same way Barbui did, is now described as one with lacking effectiveness, simply based on a problematic definition of effectiveness and over interpreting effectiveness in a one-sided way.

The most critical paper on the efficacy and effectiveness of antidepressants was recently published by Pigott et al[44] summarizing selected meta-analytical results on efficacy, predominantly the meta-analysis by Kirsch et al,[7] and the results of the STAR*D study, a so-called "real-world study".[43] The efficacy results of the STAR-D study were interpreted as effectiveness results because they included "real world", not Phase III patients. Apparently, the authors did not notice that the STAR*D patients do not reflect the average "real-world" patients, but preferably a selection of semi-chronic, partially drug refractory patients, thus leading to interesting results primarily for this subgroup of patients.[47] Overemphasizing the results of the Kirsch meta-analysis and the STAR*D study, the authors come to the overcritical conclusion that antidepressants "fail to result in sustained positive effects for the majority of people who receive them"[44].

Are all antidepressants the same in their clinical efficacy and effectiveness?

It has already been mentioned before that even in the data set of the Kirsch meta-analysis there were some differences between the investigated antidepressants, among others in the sense that e.g. venlafaxine and paroxetine demonstrated a mean difference of the pre-post changes between verum and placebo above 3.

There is not enough space here to describe results of individual studies. Therefore, only a condensation of the results of individual studies in meta-analyses, which are seen in evidence-based medicine (EBM) as the best approach to prove efficacy, are discussed. Although this view has to be critically reflected (17) for pragmatic reasons, we follow this approach here. Several meta-analyses on published results and pooled analyses on original data were performed in the recent past, especially focusing on the question of whether SSRIs are equivalent to TCAs in efficacy, whether SSRIs are better tolerable than TCAs, whether certain modern antidepressants like the selective noradrenalin/serotonin reuptake inhibitors or the allosteric serotonin reuptake inhibitor escitalopram have superior efficacy to SSRIs.[48] Most of them use the depression mean score difference of a standardised rating scale – for example, the HAM-D or the MADRS[49] as the outcome criterion for efficacy, some use responder or remitter rates.

Only few results of meta-analyses can be mentioned here.[48] A Cochrane Collaboration meta-analysis in 2003 identified 98 trials comparing SSRIs to other anti-

depressants, with a total of 5044 SSRI-treated patients, and failed to detect any clinically significant difference in efficacy between SSRIs and TCAs (Geddes et al 2003). Another Cochrane Collaboration meta-analysis investigated the tolerability and efficacy of the TCA amitriptyline in comparison with other antidepressants and SSRIs, and found no difference in overall efficacy between amitriptyline and either other TCAs or the SSRI comparators, but tolerability and acceptability measures favoured SSRIs.[50] An almost classical example is the meta-analysis by Anderso.[51] which comprised 102 randomised controlled trials including 10.706 patients. Overall, no difference in efficacy was found between SSRIs and TCAs; however, TCAs seemed to be more efficacious than SSRIs in inpatients. Regarding tolerability, Anderson looked at 95 randomised controlled studies including a total of 10,553 patients. The SSRIs were described to be better tolerated than the TCAs, with a significantly lower overall rate of treatment discontinuations and of treatment discontinuations due to side-effects, although this did not apply to fluvoxamine. A Cochrane Collaboration review identified 136 randomised trials in which SSRIs and TCAs were compared among depressed patients, and found a modest but significant difference favouring SSRIs in terms of discontinuation of treatment.[52]

Recent meta-analyses and reviews focussing on selective serotonin/noradrenalin reuptake inhibitors like venlafaxine, duloxetine and milnacepran, as well as on the noradrenergic and specific serotonergic antidepressant mirtazapine, gave hints towards a superior efficacy of these so-called "dual" antidepressants in comparison to SSRIs. But the results were inconsistent.[53,54] Surprisingly, also the SSRI escitalopram, the active s-enantiomer of the racemat citalopram, was found to be more effective than the racemat in equivalent doses, hypothetically explained[55] by the inhibiting effect of R-citalopram at an allosteric transporter binding sector.[56–65]

With tolerability as such an important issue (especially in relation to effectiveness), when it comes to the question of whether SSRIs are preferable to TCAs, also the results of the meta-analyses of Trindade et al[66] shall be mentioned in short. Trindade et al compared the side-effect profile of SSRIs and TCAs meta-analytically. Eighty-four comparative studies were included. In this meta-analysis many adverse events occurred statistically more often with at least one of the included SSRIs than with TCAs, namely nausea, "anorexia", diarrhoea, insomnia, nervousness, anxiety and agitation (which indicate the typical SSRI side effect profile). The SSRI-associated adverse effects seem to be related to drug dose, since they may reflect a functional increase in central 5-HT activity or 5-HT sensitivity. The TCAs are closely associated with medically more relevant adverse events like postural hypotension, cardiac conductance disturbances, glaucoma and urinary retention. These are not reflected in this and other meta-analyses because they refer primarily/only to rating scale data which do not include these kinds of side effects. It should be considered that the latter described side effects are of much greater clinical importance and medical relevance than the SSRI-associated symptoms described above.[48] Taking into consideration the recently approved antidepressant agomelatine it has to be stated that this AD is apparently the one with the lowest rate of any side effects.[67] Differences related to suicidality can not be discussed here due to space reasons; the reader will find respective papers in the literature.[68–70]

Cipriani et al[71] recently performed a so-called "multiple-treatment" meta-analysis (indirect meta-analysis) which enabled them to describe a full picture of the different efficacy/tolerability profiles of single antidepressants, even if, for example, drug B was never directly tested against drug C, but both only against drug A. Based on a comparison of 12 new-generation antidepressants, the authors came to the conclusion that, considering both efficacy and non-discontinuation (as proxy for acceptability) escitalopram is the most preferable drug, followed by sertraline. Taking price issues into account sertraline was eventually placed first rank because this medication costs less than escitalopram. However, this meta-analysis did not include placebo arms of controlled studies which, together with other methodological issues, are considered problematic[72] (table 1).

Apart from differences based on clinical evaluations and respective meta-analyses brain imaging can help us to gain additional insight into the different effects of antidepressants in terms of brain functioning and networks involved.[73] This might be a future way for a better understanding of the differences in efficacy and effectiveness of antidepressants.

Table 1. Efficacy and acceptability using fluoxetine as reference compound[71]

	Efficacy (response rate) OR (95% CI)	*Acceptability (dropout rate) OR (95% CI)*
Bupropion	0.93 (0.77–1.11)	1.12 (0.92–1.36)
Citalopram	0.91 (0.76–1.08)	1.11 (0.91–1.37)
Duloxetime	1.01 (0.81–1.27)	0.84 (0.64–1.10)
Escitalopram	0.76 (0.65–0.89)*	1.19 (0.99–1.44)
Fluvoxamine	1.02 (0.81–1.30)	0.82 (0.62–1.07)
Milnacipran	0.99 (0.74–1.31)	0.97 (0.69–1.32)
Mirtazapine	0.73 (0.60–0.88)	0.97 (0.77–1.21)
Paroxetine	0.98 (0.86–1.12)	0.91 (0.79–1.05)
Reboxetime	1.48 (1.16–1.90)*	0.70 (0.53–0.92)*
Sertraline	0.80 (0.69–0.93)*	1.14 (0.96–1.36)
Venlafaxine	0.78 (0.68–0.90)	0.94 (0.81–1.09)

OR=odds ratio, CI=credibility interval, *P<0.05. For efficacy, OR higher than 1 favours fluoxetine. For acceptability, OR lower than 1 favours fluoxetine

Προβλήματα σχετικά με τον καθορισμό της αποτελεσματικότητας και της δραστικότητας των αντικαταθλιπτικών φαρμάκων

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Τα αντικαταθλιπτικά φάρμακα παίζουν τον κύριο ρόλο στη θεραπεία των ασθενών με κατάθλιψη όχι μόνο λόγω του γεγονότος ότι υποβάλλονται στις πλέον εκτεταμένες δοκιμασίες για την απόδειξη της δραστικότητάς τους αλλά και στο γεγονός ότι είναι εύκολη η χρήση τους στην καθημερινή κλινική πράξη. Σχεδόν όλοι οι ψυχίατροι και οι γενικοί ιατροί που θεραπεύουν καταθλιπτικούς ασθενείς συμφωνούν πάνω στη χρησιμότητα των αντικαταθλιπτικών για τη θεραπεία των ασθενών αυτών. Ωστόσο, πρόσφατα μια σειρά από μετα-αναλύσεις αμφισβήτησε την πεποίθηση αυτή και πρόσφατα τέθηκε προς συζήτηση στον χώρο της ψυχιατρικής και της κλινικής ψυχοφαρμακολογίας το κατά πόσον η δραστικότητα των αντικαταθλιπτικών έχει κλινική αξία. Παρά το γεγονός ότι για όλα τα φάρμακα έχει κριθεί ότι διαθέτουν επαρκή δεδομένα ώστε να τους δοθεί έγκριση από το FDA και EMEA καθώς και από άλλους οργανισμούς παγκοσμίως, μερικοί συγγραφείς προχώρησαν παραπέρα και αμφισβήτησαν την αποτελεσματικότητα των αντικαταθλιπτικών φαρμάκων. Ακόμα περισσότερο, πρότειναν ότι «εναλλακτικές» θεραπείες με αναπόδεικτη αποτελεσματικότητα ή και με αποδεδειγμένη έλλειψη αποτελεσματικότητας θα πρέπει να προτιμούνται σε σχέση με τα αντικαταθλιπτικά. Αυτοί οι συγγραφείς δεν έλαβαν υπόψη τους ότι για μεθοδολογικούς λόγους δεν είναι αποδεκτό να εξάγει κανείς υπερβολικά εκτενή συμπεράσματα. Μερικές υποθέσεις στις οποίες βασίζονται, όπως η πρόταση του NICE, το οποίο θεωρεί ότι μία μέση διαφορά 3 βαθμών HAM-D μεταξύ placebo-δραστικής ουσίας έχει κλινική αξία, και είναι σαφώς αυθαίρετη με βάση τη στατιστική και δεν βασίζεται ούτε σε εμπειρικά δεδομένα ούτε στην άποψη ειδικών. Φαίνεται ότι η διαφορά στη βαθμολογία HAM-D μεταξύ της δραστικής ουσίας και του placebo είναι μεταξύ 2 και 3, και ενδεχομένως κάποιες ουσίες να εμφανίζουν ελαφρά καλύτερη απόδοση σε σχέση με άλλες. Είναι ασαφές το κατά πόσον η αρχική βαρύτητα καθορίζει την απάντηση. Υπάρχουν διαφορετικές προσεγγίσεις. Ωστόσο, πολύ σημαντικότερα για την εκτίμηση της κλινικής αξίας είναι τα αποτελέσματα που αφορούν την ανάλυση απάντησης/ύφεσης, η οποία συγκρίνει τη σχετική συχνότητα των κατηγοριών αυτών μεταξύ placebo και δραστικής ουσίας. Η προσέγγιση αυτή έχει ως αποτέλεσμα έναν Αναγκαίο Αριθμό προς Θεραπεία (number needed to treat, NNT) ίσο με 5–7. Στη Βασισμένη σε Δεδομένα Ιατρική (Evidence Based Medicine) ένας παρόμοιος NNT παραδοσιακά θεωρείται ως σημείο μέτριας προς ισχυρής δραστικότητας και αντιστοιχεί στην ισχύ που έχουν πολλές θεραπείες αναφοράς της εσωτερικής παθολογίας. Ωστόσο, από αρκετές μετα-αναλύσεις είναι σαφές ότι όταν χρησιμοποιούνται έννοιες της Βασισμένης σε Δεδομένα Ιατρικής και των οικονομικών της υγείας που είναι μακριά από την κλινική σκέψη, εμφανίζονται προβλήματα και τα αποτελέσματα είναι πολύ δύσκολο να ερμηνευτούν με κλινικούς όρους.

Λέξεις ευρετηρίου: Κατάθλιψη, αντικαταθλιπτικά φάρμακα, αποτελεσματικότητα, δραστικότητα, ανοχή

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Review Article
Ανασκόπηση

Anxiety disorders and obesity

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Anxiety disorders are the most prevalent mental disorders in developed countries. On the other hand, obesity is recognized to be one of the greatest public health problems worldwide. The connection between body weight and mental disorders remains an open issue. Low body weight has been studied enough (anorexia nervosa is a typical example) but high body weight has not been addressed sufficiently. It is known that obesity has been related with depression. Although moderate level of evidence exists for a positive association between obesity and anxiety disorders, the exact association between these two conditions is not clear yet. The studies about this subject are quite few and they follow different methodology. Furthermore, anxiety disorders share some common elements such as anxiety, avoidance and chronicity, but they also present a great deal of differences in phenomenology, neurobiology, treatment response and prognosis. This factor makes general conclusions difficult to be drawn. Obesity has been associated with anxiety disorders as following: most of the studies show a positive relationship with panic disorder, mainly in women, with specific phobia and social phobia. Some authors have found a relationship with generalised anxiety disorder but a negative relationship has been also reported. Only few studies have found association between obesity and agoraphobia, panic attacks and post traumatic stress disorder. There has not been reported a relationship between obesity and obsessive compulsive disorder. The causal relationship from obesity to anxiety disorders and vice versa is still under investigation. Pharmacological factors used for obesity treatment, such as rimonabant, were associated with depression and anxiety. Questions still remain regarding the role of obesity severity and subtypes of anxiety disorders. Besides, it is well known that in the morbidly obese patients before undergoing surgical treatment, unusual prevalence of psychopathology, namely depression and anxiety disorders, is observed. Anxiety is also a common trait in personality disorders. There is no single personality type characteristic of the morbidly obese, they differ from the general population as their self-esteem and impulse control is lower. Obese patients present with passive dependent and passive aggressive personality traits, as well as a trend for somatization and problem denial. Their thinking is usually dichotomous and catastrophic. Obese patients also show low cooperativeness and fail to see the self as autonomous and integrated. When trying to participate in society roles they are subject to prejudice and discrimination and should be treated with concern to help alleviate their feelings of rejection and guilt.

Key words: Anxiety, anxiety disorders, obesity, personality traits

Introduction

Nowadays obesity is recognized to be one of the greatest public health problems worldwide. Obesity is considered to be a modern disease. It seems that it is rapidly spreading worldwide, not only in the western, so called developed, world but also in the third, developing, world.[1] The prevalence of obesity has considerably increased the last two decades. It is estimated that nearly half a billion of the world's population is considered to be overweight or obese.[2] At the dawn of the 21st century obesity has reached epidemic proportions. Its impact in public health is rising. It is associated with significant increases in morbidity and mortality with profound social and economic consequences. Obesity is predicted to be the number one health problem by the year 2025.[3]

Obesity is a serious and multifactorially caused disease. Genetic, social, cultural and environmental factors contribute to its genesis. Its management is a challenge for psychiatrists, psychologists, endocrinologists, dieticians and surgeons. Grade III obesity (morbid obesity, BMI>39.9) is a chronic disease with poor response to conventional therapies and high rates of relapses. Morbid obesity is associated with a variety of somatic symptoms and disorders as well as psychological, psychopathological and personality features.[4]

Psychopathology and obesity

Concerning psychopathology, early studies found few differences between obese and nonobese adults. In contrast, recent well-designed research showed an unusual prevalence of psychopathology in the morbidly obese. The most frequent finding was depression and to a lesser extent anxiety disorders.[5] However, in a recent study a negative association was shown between overweight patients and generalized anxiety disorder. Worry found in this disorder may prevent individuals from excessive food intake, which may have physical and social consequences.[6] Obese patients have the tendency to somatization; they express psychological distress through physical complaints.[7] In the study of Papageorgiou et al, a preponderance of female compared to male obese patients was found regarding depression, interpersonal sensitivity, paranoid ideation, somatization, obsessive-compulsive behavior, anxiety and hostility.[8] According to van Germert et al, obesity is often accompanied with psychological consequences, such as depression, somatization, interpersonal problems, low social adjustment and low self-esteem.[9]

It has been shown that the thinking of obese patients is characterized by cognitive distortions that could be connected with anxiety disorders. Dichotomous and catastrophic ways of thinking are the most frequent cognitive distortions seen in this group of patients. A large number of obese patients present with rigid, simplistic and sometimes moralistic ways of thinking.[7] Obese patients are confronted in their lives not only with physical but also with social problems. To deal with them they use various coping strategies. Horchner et al demonstrated that obese female patients displayed avoidance wait-and-see and passive response patterns as coping behavior experiencing their relationship as relatively unreliable and not very intimate.[10]

Anxiety disorders and obesity

Anxiety disorders are the most prevalent mental disorders in the developed world.[11] They present not only with high frequency among population, but they are also chronic. Anxiety disorders fluctuate over life cycle and they typically have ameliorations and exacerbations. Anxiety, fear, excessive worry and apprehension are their main psychological symptoms and tension, fatigue and chest dysphoria are their main physical symptoms. The impact of anxiety disorders in public health is enormous, having in mind that they are the most prevalent mental disorders. They are known to increase morbidity, mortality and they have negative contribution to quality of life.[12–14] DSM-IV classifies anxiety disorders into the following categories: panic disorder, specific phobias, social phobia, generalized anxiety disorder, obsessive-compulsive disorder and stress disorders (mainly post traumatic stress disorder).

Although moderate level of evidence exists for a positive association between obesity and anxiety disorders, the exact association between these two conditions is not clear, yet.[15] Some researchers find positive association between them but some others report no special linking.[6] The heterogeneous nature of both anxiety disorders and obesity may be one of the main reasons for these mixed results.

Given the great amount of the population that suffers from obesity or/and anxiety disorders, studies in the literature that deal with their connection are surprising few. A recent review by Gariepy et al has summarized the results on this subject.[15] Prospective studies for the effect of obesity to anxiety disorders are very few and give mixed results.[15–17] On the other hand, cross-sectional studies tend to give a weak but positive association between obesity and anxiety disorders.[15] Seven studies showed a positive association that reached statistical significance,[18–22] but five more studies showed a positive, yet not significant trend.[23–27] The largest study, performed in US by Zhao et al, used self-report for anxiety disorders (that were medically diagnosed over lifetime). BMI was calculated by self-reported weight and height. There was found a positive association between obesity and anxiety disorders. This association differed between men and women concerning body weight: it was present in obese women with BMI>30 but only in severely obese men (BMI>40).[27] Gariepy et al report after meta-analysis that the odds ratio (OR) of an association between obesity and anxiety was 1.40 (confidence intervals: 1.23–1.57). The inconsistency index was 84.3% (p-value <0.001), suggesting high level of heterogeneity. It seems that obesity is positively associated with anxiety disorders but the strength of evidence is moderate.[15]

There are some variables that could explain this heterogeneity: gender is one of them; obese women are more socially discriminated than men and this could be a reason that anxiety disorders are correlated with obesity in women presenting obese, but with smaller BMI than men.[28] The degree of obesity itself is another factor that moderates this association. In morbidly obese patients undergoing surgical treatment, unusual prevalence of psychopathology, namely depression and anxiety disorders, is observed.[8] The different subtypes of anxiety disorders is another factor giving rise to heterogeneity in results. There are differences between the subtypes of anxiety disorders concerning their association with obesity.[6,15] Panic disorder has been associated with obesity in some but not all studies.[18,21,22,26] It seems that women with panic disorder are more possible to be obese, too.[18] On the other hand, specific phobia seems to be correlated with obesity in most of the studies.[18,22,25,29] Women are more probable to report both obesity and specific phobia.[25] Social phobia follows the same characteristics: it is often associated with obesity, mostly in women.[18,21,22] Some authors have found a relationship between obesity and generalized anxiety disorder (mostly in women) but a negative relationship for men has been also reported.[6,17,18] It has been hypothesized that chronic worry and muscle tension, which are present in generalized anxiety disorder, make it for individuals more probable to lose rather gain weight.[6] Only one study has found association between obesity and agoraphobia, and post traumatic stress disorder respectively.[21,22] There has not been reported a relationship between obesity and obsessive compulsive disorder.[22]

The causal relationship from obesity to anxiety disorders and vice versa is still under investigation. Obesity may be associated with anxiety disorders through several paths. Social discrimination against obese people is a common issue.[28,30] Low self esteem is another factor leading obese people to anxiety in order to compensate in a not friendly social network.[30–32] Since they consider themselves inadequate and the environment hostile, it is obvious that they develop psychological distress, social avoidance and anxiety. The way the others see obese people can become the way they see themselves.[32] They blame themselves for being fat, they try hard to get thinner (which is usually done without planning and leads to failure) and thus eating and weight control preoccupation leads to excessive worry and anxiety.[33] Furthermore, obesity can lead to several general medical conditions, which run in a chronic way, such as asthma, cardiovascular disease and diabetes mellitus.[34–36] Distress from illness burden or pharmacological factors used for treatment could lead to anxiety or depression.[13,14,37–39] In this way, another vicious circle is born.

Another view of the issue puts anxiety disorders as the causal factor for obesity. Anxiety has been correlated with hypothalamic-pituitary-adrenal (HPA) axis dysregulation, which can result in several autonomic functions dysregulation. When this leads to increased appetite, people under stress can easily gain weight.[40–42] Additionally, some people under stress not only eat more, but they "prefer" high-sugar and high-fat foods.[42–45] Another factor that links anxiety and obesity seems to be the chronic medical conditions that are associated with anxiety.

Such conditions, as asthma or heart failure, lead to reduced functionality and very often to reduced physical activity, which is one of the main causes of obesity.[34–36]

Furthermore, the causal relationship between anxiety and obesity does not necessarily run in two directions. There can be a common, third factor that can lead both to anxiety and obesity.[15] A common genetic basis for both conditions cannot be excluded. Anxiety disorders and obesity both present with high levels of heritability.[46,47] On the other hand, environmental factors during childhood can predispose to both anxiety and obesity. It has been reported that endocrine-disrupting chemicals could affect hormonal regulation and this could play a role in obesity and in anxiety disorders.[48] Family environment has a fundamental role, too. Abuse during childhood has been found to predict obesity and anxiety disorders.[49–51] Another factor that seems to predispose to both anxiety and obesity is the presence of psychiatric disorders. Anxiety disorders are often comorbid with other psychiatric disorders, especially with some that have been found to lead to weight gain, such as mood disorders, eating disorders.[52–55] Very important but more complicated is the issue of personality disorders. Some personality traits, such as avoidant coping styles, hypersensitivity to criticism and neurocriticism are often present in individuals with both obesity and anxiety disorders[5,56–59] (see more below, in: Personality traits and obesity).

Lastly, an interesting issue is the role of pharmacological factors used for obesity treatment. One of them is rimonabant, an antagonist for cannabinoid CB_1 receptors. The endocannabinoid system is known to play a key role in mental processes, such as relaxation, amelioration of pain and anxiety and sedation initiation. It has been also reported to play an essential role in regulating appetite and metabolism to maintain energy balance. Thus, the endocannabinoid system is thought to be closely related to obesity. Rimonabant was used for obesity treatment in an effort to regulate the endocannabinoid system and though its results in weight lose were remarkable it was discontinued because it was associated with depression and anxiety.[60] This fact is conflicting in the relationship of obesity and anxiety: a pharmacological factor successfully used for obesity treatment is associated with clinically raised anxiety.

Personality traits and obesity

The examination of the psychological profile of morbidly obese patients is of interest in view of the attempts to identify variables that predict success or failure in weight loss after therapy, as well as risk factors in order to tailor effective strategies for prevention. Mainly psychological factors are discussed in the genesis of obesity. In this respect, studies addressed the question as to which personality characteristics are most frequently associated with obesity. Morbidly obese patients may present with personality traits among which are passive dependent and passive aggressive ones. Other researchers have found immaturity, poor impulse control and impaired quality of life.[5,61,62] Higher score on measures of self-doubt, insecurity, sensitivity, dependence and emotional instability have also been reported.[63] In a 20-year prospective study it was shown that being overweight appears to be a stable trait. Aggressive personality traits and sociopathy were positively associated with being overweight. According to Hasler et al, aggressive personality traits may contribute to increased food intake by favoring the immediate hedonic reward of eating.[6] Morbidly obese patients presented personality disorder features related to eccentric cluster (schizoid, paranoid)[64] and anxious cluster (compulsive, dramatic).[1,7] It has been hypothesized that high scores on the schizoid and paranoid scales coincide with the difficulties in expressing aggressive feelings and interpersonal sensitivity. On the other hand, high scores on the compulsive scales are in line with immaturity and poor impulse control that have been observed in many patients with morbid obesity.[62]

Conclusion

It is clear that the causal relationship between anxiety and obesity is not easy to be established. Anxiety is multidimensional (symptom, disorder, personality trait) and obesity is not a single condition. Its impact in quality of life varies along with differences in BMI, gender and sociocultural environment. Thus, the causal relationship between anxiety and obesity might not be straightforward. It seems that there is a positive but weak correlation between them. In order to strengthen this association prospective, well designed studies will be needed.

Αγχώδεις διαταραχές και παχυσαρκία

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Οι αγχώδεις διαταραχές είναι από τις συχνότερα εμφανιζόμενες διαταραχές στον αναπτυγμένο κόσμο. Από την άλλη μεριά, η παχυσαρκία φαίνεται να αποτελεί ένα από τα μεγαλύτερα προβλήματα δημόσιας υγείας παγκοσμίως. Η σχέση του σωματικού βάρους με την εμφάνιση ψυχοπαθολογίας είναι ένα θέμα ανοιχτό προς διερεύνηση. Ενώ τα πράγματα είναι πιο συγκεκριμένα για το χαμηλό σωματικό βάρος (π.χ. ψυχογενής ανορεξία), δεν έχουν διερευνηθεί αρκετά όσον αφορά το υψηλό σωματικό βάρος. Είναι γνωστό ότι η παχυσαρκία σχετίζεται με την κατάθλιψη. Για τις αγχώδεις διαταραχές και την παχυσαρκία, όμως, τα πρώτα στοιχεία δείχνουν μια πιθανή θετική σύνδεση, αλλά η σχέση μεταξύ των δύο καταστάσεων δεν έχει αποσαφηνισθεί αρκετά. Οι μελέτες που ερευνούν το θέμα είναι σχετικά λίγες και η μεθοδολογία τους ετερογενής. Ένας παράγοντας που δυσκολεύει την εξαγωγή συμπερασμάτων για τις αγχώδεις διαταραχές συνολικά είναι και η ετερογένεια των διαταραχών που απαρτίζουν αυτή την ομάδα. Η παχυσαρκία έχει συνδεθεί με τις αγχώδεις διαταραχές ως εξής: περισσότερες μελέτες αναδεικνύουν θετική συσχέτιση με τη διαταραχή πανικού, κυρίως στις γυναίκες, τη διαταραχή κοινωνικού άγχους και τις ειδικές φοβίες. Όσον αφορά τη διαταραχή γενικευμένου άγχους, έχει αναφερθεί θετική, αλλά και αρνητική συσχέτιση. Λίγες μόνον μελέτες αναφέρουν συσχέτιση της παχυσαρκίας με την αγοραφοβία, τις κρίσεις πανικού και τη μετατραυματική διαταραχή εκ στρες. Τέλος, δεν έχει αναφερθεί συσχέτιση μεταξύ της παχυσαρκίας και της ιδεοψυχαναγκαστικής διαταραχής. Η πιθανή αιτιολογική σχέση μεταξύ της παχυσαρκίας και των αγχωδών διαταραχών και αντιστρόφως είναι ένα θέμα που παραμένει ανοιχτό προς διερεύνηση. Φαρμακολογικοί παράγοντες που έχουν χρησιμοποιηθεί για την αντιμετώπιση της παχυσαρκίας, όπως η ριμοναμπάτη, έχουν συσχετισθεί με την εμφάνιση κατάθλιψης και άγχους. Ερωτηματικά παραμένουν, ακόμη, για τον ρόλο που παίζει η βαρύτητα της παχυσαρκίας και ο τύπος της αγχώδους διαταραχής στη διασύνδεση μεταξύ των δύο καταστάσεων. Είναι γνωστό, άλλωστε, ότι στους ασθενείς με κακοήθη παχυσαρκία οι οποίοι πρόκειται να υποβληθούν σε χειρουργική θεραπεία παρατηρούνται υψηλά ποσοστά κατάθλιψης και αγχωδών διαταραχών. Το άγχος αποτελεί, επίσης, ένα σύνηθες σύμπτωμα στις διαταραχές προσωπικότητας. Δεν υπάρχει ένα μοναδικό προφίλ προσωπικότητας που να συνδέεται με την κακοήθη παχυσαρκία, αλλά αυτοί οι ασθενείς εμφανίζουν περισσότερο από τον γενικό πληθυσμό χαμηλή αυτοεκτίμηση και δυσκολότερο έλεγχο των παρορμήσεων. Παρουσιάζουν εξαρτητικά και παθητικο-επιθετικά στοιχεία προσωπικότητας, καθώς και μία τάση να σωματοποιούν ή/και να αρνούνται το πρόβλημα. Συχνά η σκέψη τους είναι διχοτομική και καταστροφολογική. Οι παχύσαρκοι ασθενείς εμφανίζουν χαμηλή συνεργατικότητα και δυσκολεύονται να δουν τον εαυτό τους ως αυτόνομο και ολοκληρωμένο. Τέλος, σημαντικό στοιχείο αποτελεί το γεγονός ότι τα παχύσαρκα άτομα αποτελούν αντικείμενο προκατάληψης και διακρίσεων γενικότερα στην καθημερινή τους ζωή. Γι' αυτό τον λόγο η θεραπευτική προσέγγιση οφείλει να προσπαθεί να ανακουφίσει τα αισθήματα ενοχής και απόρριψης που νιώθουν.

Λέξεις ευρετηρίου: Άγχος, αγχώδεις διαταραχές, παχυσαρκία, στοιχεία προσωπικότητας

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Research article
Ερευνητική εργασία

Psychotropic medication use in children and adolescents in an inpatient setting

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Medication can be an effective part of treatment for several psychiatric disorders of childhood and adolescence but its use should be based on a comprehensive psychiatric evaluation and treatment plan. The aim of this study was to evaluate psychotropic medication use for children and adolescents treated as inpatients and to compare it with principles of rational pharmacotherapy, thus identifying possible downsides of current practices and pointing a way towards safer and more efficient practices. This is a descriptive study of prescribing trends at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade, during the period from September 2009 to September 2010. Analyzed demographic data (age, gender) and the number of hospitalizations were obtained from medical histories, while diagnoses were obtained from discharge notes. Prescribed therapy was copied from medication charts. Drug dosages were analyzed as average daily doses prescribed during the hospitalization. Psychiatric diagnoses were classified according to The International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). During the examined time period, 264 patients were hospitalized (61.4% males), with an average age of 11.4±5.1 years. We have found that 66.3% of admitted patients were treated with pharmacotherapy in addition to other treatment modalities. There was a highly significant correlation between the age of patients and the prescribed dosage (Spearman's rho=0.360, p<0.001) as well as the number of prescribed drugs (Spearman's rho=0.405, p<0.001). The most commonly diagnosed psychiatric disorders were: autism spectrum disorders (20.8%), conduct disorders (19.7%), mixed developmental disorder (14.8%), adjustment disorder (7.2%), mental retardation (7.2%), acute psychosis (4.5%), and ADHD (2.3%). The most commonly prescribed medications were antipsychotics (45.9%), followed by antidepressants (17.2%), mood stabilizers (16.1%), benzodiazepines (14.4%), and other psychotropic drugs (6.4%). The most commonly prescribed antipsychotic was risperidone, used for more than 50% of the patients treated with antipsychotics. Taken together risperidone and chlorpromazine were more than 75% of all prescribed antipsychotics. 98.4% of prescribed antidepressants belonged to the SSRIs, with sertraline and fluoxetine accounting for almost 90% of them. All prescribed dosages were in accordance with the official guidelines. This is the first survey in Serbia to document the practice of prescribing psychotropic medication in the field of child and adolescent psychiatry. Current drug-prescribing practices at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade are in accordance with current practices in the United States and Europe. Not every child with symptoms of mental health problems needs pharmacological treatment; when they do, the general rule of thumb should be "start low, go slow, and taper slowly". Follow-up studies are necessary to assess the change of trends, as well as studies in different patient populations and health centers, in order to globally evaluate psychotropic medication use in children and adolescents in Serbia.

Key words: Phsychopharmacology, medication, children, adolescents, inpatients

Introduction

Pediatric psychopharmacology is a field in rapid growth according to the expanding research and regulatory action. At the same time, this area is frequently the object of different and controversial debates in the media and the general public because of the very delicate issue concerning the application of psychotropic agents in treatment of children and adolescents with mental disorders.

Key elements in the field of pediatric psychopharmacology include the specificities of the child development (in particular, the developing brain), psychopathology, chemical compounds that act on the brain, and the therapeutic objectives. Because of that, clinicians must integrate information from variety of sources in order to achieve coherent conclusions about treatment effects. However, pharmacological treatment during childhood and adolescence when the organism undergoes marked developmental changes may result in toxicities not seen in adults.[1,2] The administration of agents acting on neurotransmitter systems in rapid development may interfere with normal processes and result in unwanted long-lasting changes.

Even though psychotropic drugs are increasingly more present in the treatment of psychiatric disorders of children and adolescents, the efficacy and safety have been tested in only several groups of drugs. The vast majority of psychotropic drugs are still prescribed "off-label".[3–5] The off-label use of drugs is not in itself an inappropriate practice, because it is often supported by considerable empirical evidence and is consistent with treatment guidelines. However, it is important to inform parents that medication is going to be prescribed off-label before making treatment decisions for their child.

Testing the safety and efficacy of psychotropic drugs in child psychiatry is particularly significant because of the huge differences in the metabolism of certain drugs that were discovered in different age groups, i.e. a varying absorption rate, metabolism and excretion rates, frequently leading either to sub-dosing of medication or pronounced side-effects.[6]

The decision to use psychotropic agents has to be grounded on a good diagnosis with the aim to improve the patient's well-being and to enable his or her optimal growth and development.[3] The general rule of thumb for introducing medication to children and adolescents is "start low, go slow, and taper slowly".[7]

Pharmacoepidemiological analyses of the use of medication world-wide have shown great differences in frequency of prescribing medication in clinical practice in different countries or even different mental health centers of the same country, depending on the predominant theoretical approach, medication prices, or availability of drugs on the market.[6] For example, two thirds of antipsychotic medication prescribed to children and adolescents in the USA belong to the class of atypical antipsychotics, whereas the same class of drugs is prescribed in only 5% of cases in Germany.[5] Over 70% of children and adolescents with mental health problems in Australia are receiving two or more psychotropic drugs simultaneously, while only 5% of child psychiatrists prescribe stimulants and antipsychotics to children younger than 3 years. Roughly around 40% of indications for prescribing are off-label indications.[8]

According to existing data, there is a trend of prescribing atypical antipsychotics (risperidone, clozapine) as well as an increase of antidepressant prescriptions in Serbia's adult population.[9] An assessment of drug prescribing trends in Serbia's child and adolescent population is necessary in order to evaluate current therapeutic practice and to compare it with principles of rational pharmacotherapy worldwide, thus identifying possible downsides of current practices and point a way towards safer and more efficient practices.[5,10]

Materials and method

This is a descriptive study of prescribing trends at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade, Serbia, during the period from September 2009 to September 2010.

Analyzed demographic data (age, gender) and the number of hospitalizations were obtained from medical histories, while diagnoses were obtained from discharge notes. Prescribed therapy was copied from medication charts. Drug dosages are presented as average daily doses prescribed during the hospitalization. Dosages are analyzed and compared to the recommended daily dose, average age of patients, as well as to gender and number of previous hospitalizations.

Psychiatric diagnoses are classified according to The International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10),[13] while drugs

are classified according to The Anatomical Therapeutic Chemical (ATC) Classification System.[14]

The study was approved by the Ethical Committee of the Institute of Mental Health.

Data were analyzed using descriptive and analytical statistical methods (t-test, Spearman correlation test) using the SPSS 16.0 software.

Results

During the examined time period, 264 inpatients were treated at the Clinical Department for Children and Adolescents, 61.4% of which were male, and 38.6% female. Of the total number of inpatients in the studied period, 66.3% that were treated with psychotropic agents in addition to other treatment modalities were included in the study.

The average age of inpatients was 11.40 years (SD=5.09) ranging from 3 to 17 yeas. On average, male patients were younger (10.17 years; SD=4.79) than females (13.35 years, SD=4.16); the difference is statistically highly significant (t=5.14, p<0.01). Average number of hospitalizations per patient was 1.91 (SD=2,557), ranging from 1 to 32. No significant statistical difference was found in number of hospitalizations per gender.

There was no significant difference in drug dosing nor the number of prescribed psychotropic drugs per gender. However, there was a highly significant correlation between the age of patients and the prescribed dosage (Spearman's rho=0.360; p<0.001). When the number of prescribed drugs were compared with the patient age, a positive, highly significant correlation was found (Spearman's rho=0.405; p<0.001).

The most commonly diagnosed psychiatric disorders were: autism spectrum disorders (20.8%), conduct disorders (19.7%), mixed developmental disorder (14.8%), adjustment disorder (7.2%), mental retardation (7.2%), acute psychosis (4.5%), and ADHD (2.3%).

The most commonly prescribed medications were antipsychotics (45.9%), followed by antidepressants (17.2%), mood stabilizers (16.1%), benzodiazepines (14.4%), and other psychotropic drugs (6.4%)

Table 1 shows the most frequently prescribed drugs. The most commonly prescribed antipsychotic was risperidone, used for more than 50% of the patients treated with antipsychotics. Taken together risperidone and chlorpromazine were more than two thirds of all prescribed antipsychotics. Two most commonly used antidepressants, sertraline and fluoxetine, accounted for almost 90% of all applied antidepressants.

Our analysis has shown that 6.4% of prescribed drugs did not belong to any of the mentioned categories – 30% of those was methylphenidate (average dose was 30.12 mg; SD=0.27), 54.2% was biperiden with an average dose of 1.92 mg (SD=0.27), zolpidem in 8.3% (average dose of 5 mg), as well as propranolol in 4.2%, dosed at 30 mg per day.

Antidepressants were most commonly prescribed for the following diagnoses: F92 (31.1%), F43 (24.6%), F42 (11.5%). The most frequent indications for antipsychotics were F92 (22.3%) and F84 (18.0%). The total amount of antipsychotics prescribed for disorders from the psychotic spectrum (F20–F29) was 13.6%, while 27.3% of mood stabilizers were prescribed for patients diagnosed as F92; 18.2% was prescribed for F84, and 9.1% for F70. As for mood stabilizers, in 4.5% they were prescribed for the bipolar disorder – sodium valproate, carbamazepine, and lamotrigine account for 98.3% of used stabilizers.

Discussion

This is the first survey in Serbia to document the practice of prescribing psychotropic medication in the field of child and adolescent psychiatry.

The results of our study have shown that two thirds of inpatients during the studied period of time were treated with a combination of psychotropic drugs and other treatment modalities –individual, group, and occupational therapy– whereas one third of patients were not treated with medication at all. Younger patients were given smaller doses and fewer drugs, with dosages and the number of prescribed drugs increasing with age. These findings are consistent with the "start low, go slow" dosing principle, as well as with the caution advised when prescribing psychotropic drugs for younger children.[3,7]

We have found that a wide range of psychotropic medication has been prescribed on a regular basis, with antipsychotics being the most prescribed drugs, which is not consistent with studies conducted in countries such as Australia or USA, reporting that stimulants are by far the most commonly prescribed drugs.[7,8] Antipsychotics are most commonly prescribed for conduct disorders and autism, as well as for psychotic disorders, all of which are official indications. All pre-

Table 1. Most frequently prescribed psychotropic agents at the Clinical Department for Children and Adolescents

Drug	*(%)*	*Dosage (mg)*	*SD*
Antipsychotics			
Chlorpromazine	20.9	69.18	28.39
Risperidone	56.4	2.44	7.49
Haloperidol	7.6	2.08	1.37
Levopromazine	4.1	104.69	85.03
Olanzapine	1.2	6.25	1.77
Clozapine	5.2	188.89	123.82
Quetiapine	2.3	38.75	10.31
Fluphenazine	2.3	2.75	1.50
Antidepressants			
Sertraline	65.6	70.62	36.64
Paroxetine	8.2	20.00	0.00
Fluoxetine	23.0	20.00	0.00
Escitalopram	1.6	10.00	0.00
Mianserin	1.6	30.00	0.00
Mood Stabilizers			
Carbamazepine	18.3	327.27	228.43
Lamotrigine	21.7	78.85	58.72
Sodium valproate	58.3	786.14	533.42
Topiramate	1.7	325.00	0.00
Benzodiazepines			
Lorazepam	55.8	3.12	2.51
Diazepam	28.8	9.77	5.35
Alprazolam	3	68.58	118.140
Clonazepam	5	2.40	0.89

scribed doses were within the recommended range.[6,7] Almost two thirds of antipsychotics belonged to the second generation atypical antipsychotics, which is in accordance with trends shown in adult psychiatric population in Serbia.[9] Worldwide trends vary with similar percentage of atypical antipsychotics prescribed in the USA.[5]

Chlorpromazine, a low-potency phenothiazine, makes up for 20.9% of total antipsychotics prescribed. Although nowadays it is considered a second choice medication for psychotic disorders, chlorpromazine was used to manage agitation, which justifies its extensive use. However, because of its well known anticholinergic and sedative side-effects, and its greater potential to produce hypotension and lower the seizure threshold than haloperidol, it ought to be used with caution.[4,7]

The second most frequently prescribed class of drugs in our study were SSRIs, shown to have reliable efficacy and a good safety profile when used for treating children and adolescents. Clinical studies have confirmed that fluoxetine has the largest effect size, yet it is the third most commonly prescribed SSRI in our study. Knowing that all antidepressant drugs have significant risk when given to children and young people, fluoxetine is the only antidepressant for which clinical trial evidence shows that the benefits outweigh the risks.[15]

All of the prescribed antidepressants were dosed within recommended dose ranges.[6,7] Even though two thirds of used antidepressants were prescribed for official indications, the single most common diagnosis for which they were prescribed was the mixed emotional and conduct disorder (F92), for which antidepressants are not officially indicated. Significant acting out frequently occurs among children and adolescents with major depression and dysthymic disorder, so there are many common symptoms in the groups of conduct and affective disorders in children and adolescents. Also, the co-existence of major depression with conduct disorder increases the risk of impulsive suicidal behavior.[14]

The mood stabilizers were most commonly prescribed for conduct disorders, and only rarely for bipolar disorder, even though it is the main indication for this class of drugs. This discrepancy is due to the fact that conduct disorders make up a larger percent of inpatients. The modes of prescribing mood stabilizers were in accordance with international guidelines.[6,7] However, the most frequently used mood stabilizer, sodium valproate, is associated with several serious side-effects, such as polycystic ovary syndrome, weight gain, as well as CNS toxicity.[4,7]

Benzodiazepines make up for only 14.4% of prescribed psychiatric medication for children and adolescents, a conspicuously smaller percentage than the one found in Serbia's adult psychiatric population. Also, most commonly prescribed drug from this group was lorazepam, whereas for adults it is diazepam.[9]

The limitation of our study was that our results are not generalizable. In order to have a more precise picture of child and adolescent psychopharmacological trends in Serbia it would be necessary to study other mental health centers as well. Beside this, it should be kept in mind that hospitalization is required for serious and otherwise unmanageable patients, and that, very likely, this sample doesn't represent the population of outpatients. In the future, follow-up studies are necessary to assess the change of trends, as well as studies in different patient populations and health centers, in or-

der to evaluate in greater detail current child and adolescent psychotropic medication practices in Serbia.

Conclusion

Our findings have shown that current drug-prescribing practices at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade, Serbia are in general accordance with current therapeutic practices in the United States and Europe.

Psychotropic medication should not be offered to a child or a young person with a mental disorder except in combination with a psychological treatment. It is well known that not every child with symptoms of mental health problems needs pharmacological treatment; when they do, the general rule should be "start low, go slow." However, the prescribing psychiatrist should monitor the child or young person's progress on a regular basis, carefully looking for adverse drug reactions, while continuously reviewing mental state.

The recent debate about the safety of prescribing and using the SSRI antidepressants in children has highlighted the need for careful evaluation and monitoring of the specificities of the psychopharmacological treatment. One obvious implication is that practicing rational pharmacotherapy requires integration of knowledge at different levels, including developmental psychopathology, pharmacology, drug regulations, and bioethics, as well as a considerable investment of time on the part of the treating clinician and the child's parent. Clinicians should use psychotropic drugs based on research evidence of their efficiency, those authorized in each country for age groups and indications, and in respect to each person's individual capacity to metabolize medication. Even though as mental health professionals we have a special responsibility to our youngest patients, it is very important to resist the pressure to "do something" rapidly with medication, particularly in those cases when a more patient and cautious approach is advised.

Χρήση ψυχοτρόπων φαρμάκων σε νοσηλευόμενα παιδιά και εφήβους

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Η φαρμακευτική αγωγή αποτελεί δυνητικά αποτελεσματικό συστατικό της αντιμετώπισης πολλών ψυχικών διαταραχών της παιδικής και της εφηβικής ηλικίας, αλλά η χρήση της πρέπει να έχει ως βάση την περιεκτική ψυχιατρική αξιολόγηση και τον θεραπευτικό σχεδιασμό. Σκοπός αυτής της μελέτης ήταν η αξιολόγηση της χρήσης της φαρμακοθεραπείας σε νοσηλευόμενα παιδιά και εφήβους και η σύγκρισή της με τις αρχές της λελογισμένης φαρμακοθεραπείας, ώστε να εντοπίσει πιθανές αδυναμίες των σημερινών πρακτικών και να υποδείξει για το μέλλον ασφαλέστερες και αποτελεσματικότερες πρακτικές. Πρόκειται για περιγραφική μελέτη των συνταγογραφικών τάσεων στο Κλινικό Τμήμα Παιδιών και Εφήβων του Ινστιτούτου Ψυχικής Υγείας Βελιγραδίου κατά την περίοδο από τον Σεπτέμβρη του 2009 έως τον Σεπτέμβρη του 2010. Τα δημογραφικά στοιχεία των ασθενών (ηλικία, φύλο) και ο αριθμός των νοσηλειών τους ελήφθησαν από τα ιατρικά ιστορικά τους, ενώ οι διαγνώσεις από τα εξιτήρια. Η χορηγηθείσα θεραπεία αντιγράφηκε από τις καρτέλες φαρμάκων. Οι δόσεις των φαρμάκων καταγράφηκαν ως οι μέσες ημερήσιες δόσεις κατά τη νοσηλεία. Οι ψυχιατρικές διαγνώσεις ταξινομήθηκαν βάσει του ICD-10. Κατά την περίοδο της μελέτης, νοσηλεύθηκαν 264

ασθενείς (61,4% άρρενες), μέσης ηλικίας 11,4±5,1 ετών. Βρέθηκε ότι στο 66,3% των νοσηλευθέντων ασθενών χορηγήθηκε φαρμακοθεραπεία σε συνδυασμό με κάποια άλλη θεραπεία. Υπήρχε στατιστικά σημαντική συσχέτιση ανάμεσα στην ηλικία των ασθενών και τη δόση (rho=0,360, p<0,001) καθώς και τον αριθμό των χορηγούμενων φαρμάκων (rho=0,405, p<0,001). Οι συνηθέστερες διαγνώσεις ήταν: διαταραχές του αυτιστικού φάσματος (20,8%), διαταραχές διαγωγής (19,7%), μικτή αναπτυξιακή διαταραχή (14,8%), διαταραχή προσαρμογής (7,2%), νοητική υστέρηση (7,2%), οξεία ψύχωση (4,5%), και ΔΕΠΥ (2,3%). Τα συνηθέστερα χορηγούμενα φάρμακα ήταν τα αντιψυχωσικά (45,9%), ακολουθούμενα από τα αντικαταθλιπτικά (17,2%), τα σταθεροποιητικά (16,1%), τις βενζοδιαζεπίνες (14,4%), και άλλα ψυχοτρόπα (6,4%). Το συνηθέστερα χορηγούμενο αντιψυχωσικό ήταν η ρισπεριδόνη, που δόθηκε σε άνω του 50% των ασθενών που έλαβαν αντιψυχωσικά. Η ρισπεριδόνη και η χλωροπρομαζίνη μαζί αποτέλεσαν πάνω από 75% του συνόλου των χορηγηθέντων αντιψυχωσικών. 98,4% των χορηγηθέντων αντικαταθλιπτικών ήταν SSRI, με τη σερτραλίνη και τη φλουοξετίνη να αποτελούν σχεδόν το 90% αυτών. Όλες οι συνταγογραφηθείσες δοσολογίες ήταν σε συμφωνία με τις επίσημες οδηγίες. Πρόκειται για την πρώτη μελέτη των πρακτικών συνταγογράφησης στην ψυχιατρική παιδιών και εφήβων στη Σερβία. Οι τρέχουσες συνταγογραφικές πρακτικές στο Κλινικό Τμήμα Παιδιών και Εφήβων του Ινστιτούτου Ψυχικής Υγείας Βελιγραδίου συμφωνούν με τις σύγχρονες πρακτικές στις ΗΠΑ και την Ευρώπη. Δεν απαιτείται φαρμακοθεραπεία για κάθε παιδί με συμπτώματα ψυχικής διαταραχής, στις περιπτώσεις όμως που απαιτείται ακολουθείται ο κανόνας «ξεκίνα με χαμηλή δόση, αύξησε τη δόση αργά, μείωσε τη δόση αργά». Απαιτούνται μελέτες παρακολούθησης για την εκτίμηση των μεταβολών των συνταγογραφικών τάσεων, καθώς και μελέτες σε διαφορετικούς πληθυσμούς ασθενών και κέντρα υγείας για τη συνολική εκτίμηση της χρήσης της φαρμακοθεραπείας στα παιδιά και στους εφήβους στη Σερβία.

Λέξεις ευρετηρίου: Ψυχοφαρμακολογία, φάρμακα, παιδιά, έφηβοι, νοσηλευόμενοι ασθενείς

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Research article
Ερευνητική εργασία

Fatigue in female patients with major depression: The effect of comorbid anxiety disorders

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Several studies have investigated fatigue in the general population, in primary care facilities as well as in patients with fatigue-related physical diseases, but only marginally in patients with Major Depressive Disorder (MDD). Therefore, the investigation of correlates of depression-related fatigue is highly warranted and expected to facilitate the implementation of effective fatigue-specific treatment strategies. Depressed patients often suffer from comorbid anxiety disorders (CADs) or subthreshold anxiety symptoms. This study aimed to investigate the independent correlation of the severity of fatigue in female patients with MDD with the presence, number and type of CADs. We studied 70 consecutive female MDD patients (48.6% inpatients), aged 23–65 years (mean 48.2±10.6 years), currently in a Major Depressive Episode [17-item Hamilton Depression Rating Scale (HDRS) score≥17] and free of other fatigue-associated conditions. Diagnostic assessments were made with the short structured DSM-IV-based MINI version 5.0.0. Reported fatigue was assessed with the 14-item Chalder Fatigue Questionnaire (FQ). Correlations between the FQ score and age, inpatient status, HDRS score, presence and number of CADs were calculated. Then, stepwise multiple regression analyses were performed, with the FQ score as the dependent variable, so as to isolate independent predictors of the severity of fatigue. 92.9% of patients had clinically significant fatigue. 62.9% were suffering from at least one CAD (38.6% met criteria for one CAD, 21.4% for two and 2.9% for three). 51.4% were diagnosed with generalized anxiety disorder (GAD), 25.7% with panic disorder and/or agoraphobia (PD/AP), 17.1% with social anxiety disorder and 7.1% with obsessive-compulsive disorder. The FQ score was significantly correlated with the HDRS score ($r=0.406$, $p<0.001$), the presence of any CAD(s) (rho=0.4, p=0.001), the number of CADs (rho=0.393, p=0.001), the presence of GAD (rho=0.421, $p<0.001$) and the presence of PD/AP (rho=0.252, p=0.035). In multiple regression analyses, the presence and number of CADs and the presence of comorbid GAD turned out as significant independent predictors of the FQ score along with the HDRS score. The severity of fatigue in female MDD patients is independently correlated with the presence and number of CADs and, in specific, comorbid GAD. Our findings imply that: (1) this effect might in part account for greater impairment/disability and adverse prognosis for MDD with CADs; (2) high levels

of fatigue, putatively clustering with anxiety symptoms, may be a marker of severity and anxiety disorders comorbidity for MDD and may define an "anxious-fatigued" subtype/phenotype in this population; (3) medications and psychotherapies for the management of severe depression-related fatigue should also target CADs.

Key words: Fatigue, anxiety disorders, comorbidity, generalized anxiety disorder, major depression

Introduction

Fatigue is considered a core symptom of major depressive disorder (MDD); its prevalence in depressed patients ranges in various studies from 73 to 94%.[1,2] Fatigue is also a common residual symptom of depressive disorders with a slow and poor response to antidepressant treatment[3] and a major risk factor of chronicity of MDD.[4] Moreover, the severity of reported fatigue is a key predictor of quality of life and social and occupational functioning in MDD patients.[5] However, fatigue in these patients has been studied far less than in other fatigue-related conditions. Several studies have investigated fatigue in the general population, in primary care facilities as well as in patients with fatigue-related physical diseases, but only marginally in MDD patients;[6] the severity of fatigue in these patients has been found to correlate with the severity of depression,[7,8] sleep disturbances[9] and female gender.[10] Therefore, the investigation of correlates of depression-related fatigue is highly warranted and expected to facilitate the implementation of effective fatigue-specific treatment strategies.

Depressed patients often suffer from comorbid anxiety disorders or subthreshold anxiety symptoms.[11,12] In fact, the term "anxious depression" has been coined to describe the highly prevalent co-occurrence of depression and anxiety spectrum disorders.[13] Assessment of co-morbid anxiety in patients with depression is of great importance since patients with both anxious and depressive symptoms have been shown to have poorer clinical outcomes, a worse prognosis, a more protracted course of illness, worse psychosocial functioning, and decreased response and compliance to treatment.[14–17] The objective of this study was to investigate the independent correlation of the severity of fatigue in female MDD patients with the presence, type and number of comorbid anxiety disorders (CADs).

Material and method

Subjects

Subjects participating in the study were consecutive female patients, aged 18–65 years, who were either hospitalized in one of the wards of the Psychiatric Clinic, or treated at the outpatient service of the Eginition Hospital, University of Athens; all of them had a main diagnosis of MDD and were currently in a Major Depressive Episode (MDE), as assessed by the same examiner-psychiatrist (PF) with the short structured DSM-IV-based Mini International Neuropsychiatric Interview (MINI) version 5.0.0.[18] Moreover, all patients had a 17-item Hamilton Depression Rating Scale (HDRS)[19] score ≥17.[20] Patients' clinical diagnosis (of MDD and specific CADs) was verified by an independent chief psychiatrist (VK) according to DSM-IV criteria. Demographic (age, employment status, education, family status) and clinical characteristics (MDD duration, age at onset, number of MDEs, duration of current MDE, chronicity, lifetime number of suicide attempts and lifetime number of psychiatric hospitalizations) of patients were also recorded.

Patients were excluded if: (1) additional diagnoses or specifiers interfered with cooperation in the study (catatonic or psychotic features in the present episode, organic mental disorders, mental retardation), (2) they met criteria for other DSM-IV axis I mental disorders potentially associated with clinically significant fatigue (except anxiety disorders), (3) they suffered from severe fatigue-associated physical diseases (e.g., infections, neoplasms, rheumatic, haematological, endocrine diseases, etc.), (4) other fatigue-related conditions were met (severe obesity with BMI>45, pregnancy, fatigue-associated medications except psychotropics), (5) a recent (i.e. less than 3 weeks ago) change in the drug treatment regimen had been effected.

All patients had their medical history recorded. A thorough physical examination was carried out and

blood was drawn for a biochemical profile, basic endocrinological tests and complete blood count within ±2 days from the clinical/psychometric evaluations. Patients were further tested once clinical evaluations and routine laboratory tests provided evidence for physical diseases potentially associated with prominent fatigue. When patients met one or more of the exclusion criteria, they did not enter the analysis. Selected patients were asked to provide written informed consent before participating in the study. The study protocol was approved by the Research Ethics Committee of Eginition Hospital.

A total of 77 patients (41 outpatients and 36 inpatients) were screened. Out of them, 2 inpatients and 2 outpatients were excluded since they suffered from a physical disease (multiple sclerosis, anemia, chronic obstructive pulmonary disease) or condition (severe obesity with BMI>45) potentially associated with clinically significant fatigue; moreover, another outpatient was excluded as diagnosed with "Bipolar II disorder, currently in a MDE", while another 2 outpatients refused to participate in the study. Subjects finally included were 70 female patients, aged between 23 and 65 years (mean 48.2±10.6 years); 34 were inpatients (48.6%). All patients were under antidepressant medication (57.1% on SSRIs and 42.9% on SNRIs).

Measures

Fatigue

The severity of fatigue reported by patients during the last two weeks prior to assessment was recorded by means of the 14-item Fatigue Questionnaire (FQ).[21] The FQ is an established, self-report fatigue questionnaire assessing the intensity of fatigue-related symptoms.[22,23] Each item is rated on a 4-point Likert scale (0 "better than usual", 1 "no more than usual", 2 "worse than usual", 3 "much worse than usual"). The FQ score is the sum of all items' scores (range 0–42). An alternative scoring method uses a bimodal response system which dichotomizes Likert scores (0, 0, 1, 1), giving a score range of 0–14. Receiver Operating Characteristics analysis has demonstrated that a cut-off of 4 or higher (3/4) best defines cases of clinically significant fatigue when the bimodal response format is used.[21] The FQ was recently standardised in MDD patients by our group.[24] Previous validity studies have confirmed a two dimension structure: a physical (FQphys: items 1–8) and a mental (FQment: items 9–14) fatigue subscale.[21]

Depression

The severity of patients' depression was assessed by the 17-item HDRS, which is one of the most widely used observer-rated instruments to assess the severity of depressive symptoms in MDD patients. Eight items are scored from 0 to 2 and nine items are scored from 0 to 4. A cut-off point of 17 is often used to ensure a degree of depression severity.[20] All ratings were completed by the same examiner-psychiatrist (PF) on the basis of patient interview (depressive symptoms experienced over the past week), information provided by relatives or nurses and observations.

Statistical analysis

Descriptive statistics were used to explore the sample's demographic and clinical characteristics. Student's independent samples t-test or Mann-Whitney U test (as appropriate) and Pearson chi-square test were used for the comparison of continuous and categorical variables, respectively, between patient subgroups. Pearson's (r) or Spearman's (rho) coefficients were then employed to calculate bivariate correlations between the FQ score as the dependent variable and the independent variables (age, inpatient status, HDRS score, presence and number of CADs), as well as in intercorrelations between the independent variables to test for collinearity. Then, stepwise multiple regression analyses were performed, with the FQ score as the dependent variable, so as to isolate independent predictors of the severity of fatigue. Whenever two independent variables had a Pearson's or Spearman's correlation coefficient ≥0.7 between them, one of them was excluded from the multivariate analysis for collinearity.[25] All statistical analyses were carried out using SPSS version 14.0 for Windows.

Results

Patient demographic and clinical characteristics

Demographic and clinical characteristics of the total sample are presented in table 1. There were no missing data regarding all measures administered. HDRS and FQ scores were approximately normally

Table 1. Demographic and clinical characteristics of the total sample (N=70) and comparison of patients with (N=44) and without (N=26) comorbid anxiety disorders

	Total sample	*MDD with CAD*	*MDD without CAD*	*Statistics*
Age (y)	48.2±10.6	47.8±10.4	48.9±11.2	ns[a]
Inpatient	48.6%	52.3%	42.3%	ns[b]
Employed	31.4%	27.3%	38.5%	ns[b]
Education (y)	10.6±4.5	10.7±4.0	10.2±5.3	ns[a]
Living alone	40.0%	36.4%	46.2%	ns[b]
MDD duration (y)	13.1±10.8	13.8±10.7	11.8±11.0	ns[a]
Age at onset (y)	35.1±12.6	34.0±12.5	37.1±12.7	ns[a]
Number of episodes	3.8±2.7	3.9±2.5	3.6±3.0	ns[c]
Duration of current episode (m)	8.9±12.8	9.5±15.5	7.7±5.9	ns[c]
Chronicity	7.1%	9.1%	3.8%	ns[b]
Lifetime number of suicide attempts	0.8±1.7	0.9±1.5	0.7±2.0	ns[c]
Lifetime number of psychiatric hospitalizations	1.5±2.4	1.6±2.4	1.4±2.4	ns[c]
HDRS	21.4±5.1	23.6±4.6	17.8±3.8	p<0.001[a]
FQ	30.4±8.0	32.9±6.5	26.1±8.6	p<0.001[a]

[a]Independent samples t-test, [b]Pearson's chi-square, [c]Mann-Whitney U test
MDD=Major Depressive Disorder, CAD=comorbid anxiety disorder(s), HDRS=Hamilton Depression Rating Scale score, FQ=Fatigue Questionnaire score, ns=non-significant, y=years; m=months

distributed. HDRS scores ranged from 17 to 33 (mean 21.4±5.1), while FQ scores ranged from 8 to 42 (mean 30.4±8.0). The mean FQphys score was 18.3±4.8 (range 7–24), while the mean FQment score was 12.0±3.8 (range 1–18). Sixty-five patients (92.9%) had fatigue of clinically significant severity, on the basis of the cut-off of ≥4 when the dichotomized item scores (bimodal response format) were used.

Forty-four patients (62.9%) were concurrently suffering from at least one anxiety disorder, as assessed with the MINI; 38.6% of patients met criteria for one CAD, 21.4% for two and 2.9% for three. The prevalence of CADs diagnosed was 51.4% for generalized anxiety disorder (GAD), 25.7% for panic disorder (PD) and/or agoraphobia (AP), 17.1% for social anxiety disorder (SAD) and 7.1% for obsessive-compulsive disorder (OCD).

Comparisons between groups and correlations

Inpatients and outpatients did not significantly differ in age (t=1.72, df=68, p=0.09), HDRS score (22.6±5.3 *vs* 20.4±4.8, respectively; t=1.83, df=68, p=0.07) and FQ score (30.0±8.3 *vs* 30.8±7.7, respectively; t=0.42, df=68, p=0.67). Patients on SNRIs did not significantly differ from those on SSRIs in HDRS scores (t=1.15, df=68, p=0.26), FQ scores (t=1.93, df=68, p=0.06) and frequency of CADs (x^2=1.75, p=0.19).

Patients with CADs (N=44) did not significantly differ from those without (N=26) in age, inpatient status, education years, employment status, family status, MDD duration, age at onset, number of MDEs, chronicity, lifetime number of suicide attempts and lifetime number of psychiatric hospitalizations; however, the former had significantly higher HDRS (t=5.5, df=68, p<0.001) and FQ scores (t=3.76, df=68, p<0.001) (table 1). When patients with (N=36) and without (N=34) comorbid GAD were compared on the same set of parameters, the former had a greater number of MDEs (U test, z=2.25, p=0.025), a trend for more lifetime suicide attempts (U test, z=1.80, p=0.072) as well as higher HDRS (t=5.0, df=68, p<0.001) and FQ scores (t=3.7, df=68, p<0.001).

Bivariate (Pearsons's or Spearman's, as appropriate) correlations between FQ score, age, inpatient status, HDRS score and the presence or number of CADs are shown in table 2. The FQ score was significantly correlated with the HDRS score (r=0.406, p<0.001), the presence of any CAD(s) (rho=0.4, p=0.001), the number of CADs (rho=0.393, p=0.001), the presence of GAD (rho=0.421, p<0.001) and the presence of PD/AP (rho=0.252, p=0.035).

Multiple regression analysis

Given that the presence of any CAD(s), the number of CADs and the presence of GAD were found collinear, with intercorrelation coefficients >0.7 between them (table 2), three distinct multiple regression

Table 2. Correlations between FQ score, age, inpatient status, HDRS score, presence and number of comorbid anxiety disorders in female MDD patients.

	FQ	*Age*	*Inpatient status*	*HDRS*	*CAD*	*Number of CADs*	*GAD*	*PD/AP*	*SAD*	*OCD*
FQ	1									
Age	*–0.084* 0.491	1								
Inpatient status	–0.038 0.758	0.208 0.084	1							
HDRS	0.406(**) <0.001	0.181 0.133	0.211 0.080	1						
CAD	0.400(**) 0.001	–0.075 0.539	0.096 0.428	0.563(**) <0.001	1					
Number of CADs	0.393(**) 0.001	–0.087 0.474	0.057 0.638	0.566(**) <0.001	0.891(**) <0.001	1				
GAD	0.421(**) <0.001	–0.005 0.968	0.087 0.476	0.524(**) <0.001	0.791(**) <0.001	0.744(**) <0.001	1			
PD/AP	0.252(*) 0.035	–0.059 0.627	0.082 0.499	0.478(**) <0.001	0.452(**) <0.001	0.675(**) <0.001	0.179 0.137	1		
SAD	0.012 0.920	–0.142 0.242	0.007 0.954	–0.072 0.555	0.189 0.117	0.358(**) 0.002	0.116 0.338	0.137 0.259	1	
OCD	0.000 1.000	–0.118 0.330	–0.159 0.190	0.025 0.839	0.213 0.076	0.275(*) 0.021	–0.063 0.602	0.091 0.455	–0.068 0.574	1

Spearman's rho or Pearson's r (in bold italics) correlation co-efficients (upper line of each cell) with corresponding p-values (lower line)

*P<0.05, **P<0.01 (2-tailed)

MDD=Major Depressive Disorder; FQ=Fatigue Questionnaire score; inpatient status (0: outpatient, 1: inpatient); gender (0: female, 1: male); HDRS=Hamilton Depression Rating Scale score; CAD=comorbid anxiety disorder(s); GAD=generalized anxiety disorder, PD/AP=panic disorder and/or agoraphobia; SAD=social anxiety disorder; OCD=obsessive-compulsive disorder (for CAD, GAD, PD/AP, SAD, OCD, 0: absence, 1: presence)

models with the FQ score as the dependent variable were built. In all three, age, inpatient status and the HDRS score were included among the independent variables. In the first model, the presence of any CAD(s) was also included among the independent variables and turned out as the only significant predictor of the FQ score, with a standardised beta coefficient of 0.415 ($p<0.001$, $R^2=0.172$). In the second model, the number of CADs was also included and turned out as the only significant predictor of the FQ score, with a standardised beta coefficient of 0.411 ($p<0.001$, $R^2=0.169$). In the third model, the presence of specific anxiety disorders (GAD, PD/AP, SAD, OCD) was also included; the HDRS score and the presence of GAD turned out as the only significant predictors of the FQ score, with standardised beta coefficients of 0.264 ($p=0.041$) and 0.271 ($p=0.036$), respectively, and an R^2 of 0.218. Of notice, the statistical significance and standardized beta coefficients in the three aforementioned models remained unchanged when SSRIs/SNRIs status was also included among the independent variables.

Discussion

The present study aimed to investigate the effect of CADs on the severity of fatigue in female patients with unipolar non-psychotic MDD. Patients with physical diseases or other conditions potentially associated with prominent fatigue were excluded, so that the confounding effect of other fatigue-related conditions is avoided. In general, levels of fatigue reported by patients in our sample (92.9%) are in line with data from previous studies.[1,2,7] One of the advantages of this study compared to many previous ones is that the severity of fatigue in MDD patients was

measured with a specific fatigue measure (FQ) that is the only one to have been standardized specifically for depressed patients.[24] FQ scores in our sample showed moderate correlations with the severity of depression, corroborating previous findings.[7,8] FQ scores had non-significant correlations with age, in accordance with data from previous studies.[8,10]

In general, the high comorbidity rates of MDD and anxiety disorders detected in our sample are in line with previous reports. Landmark epidemiological community surveys have reported high prevalence rates of a lifetime anxiety disorder in MDD patients: 47% in the Epidemiologic Catchment Area study;[26] 58% in the National Comorbidity Survey (NCS).[11] The ORs for comorbidity of MDD with the specific anxiety disorders were: 6.0 for GAD, 4.0 for PD and Post-Traumatic Stress Disorder (PTSD), and 2.9 for SAD (mean OR=4.2).[11] In primary care samples, comorbidity of depressive and anxiety disorders seems to be more common than either disorder alone.[27] The largest study to date to investigate clinical correlates of anxious features in MDD outpatients with a dimensional approach reported a prevalence estimate of anxious depression of 46%; patients with anxious MDD were significantly more likely to be older, unemployed, less educated and more severely depressed.[28] Studies in psychiatric, community and primary care samples have shown that MDD patients with CADs have poorer clinical outcomes, more severe symptoms, a worse prognosis, worse overall functioning, greater suicide potential, increased treatment seeking, higher frequency and intensity of side-effects, greater refractoriness and reduced compliance to treatment.[11,15,17,28–30] Recently published data from the multi-center Coordinated Anxiety Learning and Management (CALM) study in primary care outpatients showed that when the number of CADs increases, mental and physical functioning and well-being deteriorates and disability increases.[31]

Comorbidity between GAD and MDD is particularly strong. The NCS follow-up study recorded a high rate of lifetime comorbidity between the two disorders (OR=6.6).[32] Moreover, a number of primary care studies have shown that 35–50% of patients with current major depression have comorbid GAD; this is often higher than rates of other comorbid disorders.[14] Compared to depressed patients without GAD, depressed patients with comorbid GAD have an earlier age at onset, higher levels of suicidal ideation and pathological worry, poorer social functioning, and a greater frequency of other anxiety disorders, eating disorders, and somatoform disorders.[33] Community and primary care studies show that MDD comorbid with GAD is associated with more impairment and disability, compromised quality of life, greater healthcare utilization and a poorer or slower response to both pharmacotherapy and psychotherapy than MDD without GAD.[11,30,34,35]

Fatigue tends to be highly correlated with psychological distress (depression and anxiety) both in community and primary care settings.[36–38] In a factor-analytic study of depressive symptoms in MDD outpatients, lack of energy/fatigability was significantly correlated with depressive anhedonia and anxiety/irritability.[39] Several studies have assessed the impact of CADs (and/or specifically comorbid GAD) on global measures of functioning, disability or health-related quality of life (e.g. the 36-item Short-Form Health Survey) in MDD patients.[15,28,30,33] In most of these studies, a significant effect of CADs on fatigue severity can indirectly be deduced from specific items or subscales of the generic measures used. Our study is the first to investigate the effect of CADs on the severity of fatigue in MDD patients, as directly recorded with a specific fatigue measure (FQ); a main outcome was that the presence of CADs was an independent predictor of the severity of reported fatigue (FQ score) in MDD patients. This finding implies that the negative impact of CADs on the course and prognosis of MDD documented in community, psychiatric and primary care samples is in part accounted for by higher levels of fatigue reported by anxious MDD patients, as fatigue is known to predict a chronic course and early relapse of MDD.[4] Furthermore, our study recorded a "dose-response" relationship between the number of CADs and levels of fatigue in MDD patients, in line with the results of the CALM study.[31] A third finding of our study was that the presence of GAD, in specific, correlated independently with the severity of fatigue in female MDD patients, in accordance with greater impairment/disability and reduced functioning associated with MDD/GAD comorbidity in community and primary care studies.

Several lines of evidence might provide an explanation for our findings. Fatigue is a major symptom

of both MDD and GAD; therefore, when both conditions are present clinically significant fatigue is more probable to be reported. Both depression and anxiety might, as well, be considered as pathoplastic factors for fatigue through psychoneuro-endocrinological or immunological mechanisms. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and high concentrations of pro-inflammatory cytokines (such as IL-1β, IL-6 and TNF-α) associated with both chronic stress/anxiety and major depression contribute to a pro-inflammatory response in the brain.[40,41] This condition mediates most stress- and depression-related symptoms, such as sleep compromise, fatigue, anorexia and decreased libido, and forms the basis of the "sickness" hypothesis of chronic stress and depression.[40] Moreover, brain inflammation is associated with neurotoxicity and neurodegeneration of critical brain structures, putatively accounting for symptoms such as fatigue and cognitive dysfunction in affective disorders.[42] MDD patients with comorbid anxiety were shown to have a higher cortisol awakening response[43] and attenuated cortisol or adrenocorticotropic hormone (ACTH) responses to HPA axis challenge tests compared to patients with "pure" depression.[44] However, no study has yet compared cytokine profiles of MDD patients with comorbid anxiety and those without.

Studies in primary care and community twin samples have stressed the independence of prolonged fatigue from psychological distress (anxiety/depression), with only partial genetic covariation between them.[36,45–47] In a large multi-center study exploring the familiality of symptom dimensions in MDD, anxiety symptoms and fatigability/exhaustion loaded on two separate factors which showed the highest degrees of correlation between depressed siblings (i.e. familiality).[48] Therefore, the co-occurrence of high levels of fatigue and anxiety symptoms in a subgroup of MDD patients may define an "anxious-fatigued" subtype with possibly distinct genetic and clinical characteristics. Family and twin studies have shown that depression and anxiety disorders co-aggregate in families and share, to a considerable extent, common genetic liabilities; more specifically, MDD and GAD in females have been reported to have a genetic correlation of unity, i.e. vulnerability to both disorders is influenced by the same genetic factors.[49] Genetic pleiotropy has been proposed as an explanation for the high comorbidity rates of MDD and GAD.[50] Furthermore, first-degree relatives of patients with anxious depression have been reported to have a higher risk of depression[29] and GAD[33] compared to first-degree relatives of patients with "pure" depression (without comorbid anxiety), suggesting a higher familial prevalence and a heavier genetic loading for both depression and GAD in anxious depressed patients. Comorbid anxiety symptoms (or comorbid GAD) could, therefore, be conceptualized as familiality/heritability and severity markers for MDD.[29] According to the findings of our study, it might be hypothesized that high levels of fatigue, putatively clustering with anxious phenotypes, are a marker of severity and anxiety disorders comorbidity for MDD.

A potential implication of our findings regards the rationale of therapeutic interventions needed to alleviate depression-related fatigue. Unfortunately, little solid empirical evidence is available to guide what modifications might optimize treatment of anxious depression; the first study to systematically investigate how the presence of comorbid anxiety may impact treatment planning for MDD outpatients indicated that practitioners solely tend to prescribe a greater number of psychotropics to depressed patients with comorbid anxiety.[51] Yet, there is strong evidence that while all antidepressant medications are approximately equally effective for the treatment of depression, serotonin-acting antidepressants are superior over norepinephrine-acting antidepressants in the treatment of anxiety disorders; moreover, various psychotherapies have proved effective in treating anxiety disorders.[16] Our findings imply that treatment regimes designed to manage severe fatigue-related complaints in MDD patients might be expected to include properly selected, dosaged and titrated medications as well as psychotherapeutic options which should also target CADs.

The following limitations of this study should be noted: All enrolled patients were on a stabilized antidepressant regimen (SSRIs or SNRIs) for at least 3 weeks, so that side-effects emerging during medication titration or withdrawal were avoided. Yet, fatigue and comorbid anxiety in depressed subjects under treatment may be associated both with depression per se and with its treatment. Nevertheless, recorded fatigue severity was not correlated with the kind of antidepressant received (SSRIs or SNRIs). Another limitation in this study was that only female

patients were included. Therefore, our results are not generalizable to all MDD patients. Further studies including both female and male subjects are needed in order to investigate potential sex differences or similarities of the effect of comorbid anxiety on depression-related fatigue.

In conclusion, the severity of fatigue in female MDD patients, as recorded with the FQ, is independently correlated with the presence and number of CADs and in specific comorbid GAD. This effect might in part account for greater impairment/disability, reduced functioning and adverse prognosis associated with MDD comorbid with anxiety disorders (and, in specific, GAD) documented in community, psychiatric and primary care samples. Our results lend support to the hypothesis that high levels of fatigue, putatively clustering with anxiety symptoms, are a marker of severity and anxiety disorders comorbidity for MDD and may define an "anxious-fatigued" subtype/phenotype in this population. Finally, our findings imply that medications and psychotherapies selected for the management of severe depression-related fatigue should also target CADs.

Η κόπωση σε γυναίκες ασθενείς με μείζονα κατάθλιψη: Η επίδραση των συννοσηρών αγχωδών διαταραχών

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Αρκετές μελέτες έχουν διερευνήσει την κόπωση στον γενικό πληθυσμό, στις υπηρεσίες πρωτοβάθμιας φροντίδας και σε ασθενείς με σωματικές νόσους που σχετίζονται με κόπωση αλλά μόνο περιστασιακά σε ασθενείς με Μείζονα Καταθλιπτική Διαταραχή (ΜΚΔ). Ως εκ τούτου, η διερεύνηση παραμέτρων που σχετίζονται με την κόπωση στη μείζονα κατάθλιψη είναι ζητούμενο και αναμένεται να διευκολύνει την ανάπτυξη αποτελεσματικών, ειδικών για την κόπωση θεραπευτικών στρατηγικών. Οι ασθενείς με κατάθλιψη πάσχουν συχνά από συννοσηρές αγχώδεις διαταραχές (ΣΑΔ) ή από υπο-ουδικά αγχώδη συμπτώματα. Η μελέτη αυτή είχε ως σκοπό της να διερευνήσει ανεξάρτητες συσχετίσεις της βαρύτητας της κόπωσης σε ασθενείς με ΜΚΔ με την παρουσία, τον αριθμό και τον τύπο των ΣΑΔ. Μελετήθηκαν διαδοχικά 70 γυναίκες με ΜΚΔ (48,6% νοσηλευόμενες), ηλικίας 23–65 ετών (μ.ό. 48,2±10,6), που βρίσκονταν σε Μείζον Καταθλιπτικό Επεισόδιο [βαθμολογία στην κλίμακα κατάθλιψης του Hamilton (HDRS)≥17] και δεν έπασχαν από άλλες σχετιζόμενες με κόπωση καταστάσεις. Οι διαγνωστικές εκτιμήσεις πραγματοποιήθηκαν με τη βραχεία δομημένη συνέντευξη MINI 5.0.0. βάσει των κριτηρίων του DSM-IV. Η αναφερόμενη κόπωση καταγράφηκε με το ερωτηματολόγιο 14 λημμάτων Fatigue Questionnaire (FQ) της Chalder. Υπολογίσθηκαν οι συσχετίσεις ανάμεσα στη βαθμολογία στο FQ και την ηλικία, το καθεστώς νοσηλείας ή μη, τη βαθμολογία στην HDRS, την παρουσία και τον αριθμό των ΣΑΔ. Στη συνέχεια, διενεργήθηκαν αναλύσεις πολλαπλής γραμμικής παλινδρόμησης με τη βαθμολογία στο FQ ως εξαρτημένη μεταβλητή, ώστε να απομονωθούν ανεξάρτητοι προβλεπτικοί παράγοντες της βαρύτητας της κόπωσης: 92,9% των ασθενών είχαν κλινικά σημαντική κόπωση, 62,9% έπασχαν από τουλάχιστον μία ΣΑΔ (38,6% πληρούσαν κριτήρια για μία ΣΑΔ, 21,4% για δύο και 2,9% για τρεις), 51,4% είχαν διάγνωση Διαταραχής Γενικευμένου Άγχους

(ΔΓΑ), 25,7% Διαταραχής Πανικού ή/και Αγοραφοβίας (ΔΠ/ΑΦ), 17,1% Κοινωνικής Φοβίας και 7,1% Ιδεοψυχαναγκαστικής Διαταραχής. Η βαθμολογία στο FQ συσχετίσθηκε σε βαθμό στατιστικά σημαντικό με τη βαθμολογία στην HDRS (r=0,406, p<0,001), την παρουσία οποιασδήποτε ΣΑΔ (rho=0,4, p=0,001), τον αριθμό των ΣΑΔ (rho=0,393, p=0,001), την παρουσία ΔΓΑ (rho=0,421, p<0,001) και την παρουσία ΔΠ/ΑΦ (rho=0,252, p=0,035). Στις αναλύσεις πολλαπλής γραμμικής παλινδρόμησης, η παρουσία οποιασδήποτε ΣΑΔ, ο αριθμός των ΣΑΔ και η παρουσία συννοσηρής ΔΓΑ αναδείχθηκαν ως στατιστικά σημαντικοί ανεξάρτητοι προβλεπτικοί παράγοντες της βαθμολογίας στο FQ μαζί με τη βαθμολογία στην HDRS. Η βαρύτητα της κόπωσης στις γυναίκες ασθενείς με ΜΚΔ συσχετίζεται ανεξάρτητα με την παρουσία και τον αριθμό ΣΑΔ και, ειδικότερα, με την παρουσία συννοσηρής ΔΓΑ. Τα ευρήματά μας καταδεικνύουν ότι: (1) η συσχέτιση αυτή εξηγεί πιθανώς εν μέρει τη μεγαλύτερη επιβάρυνση/αναπηρία και τη χειρότερη πρόγνωση της ΜΚΔ με ΣΑΔ, (2) τα υψηλά επίπεδα κόπωσης, που συνοδεύονται συχνά από αγχώδη συμπτώματα, αποτελούν πιθανώς δείκτη βαρύτητας και συννόσησης με αγχώδεις διαταραχές στην ΜΚΔ και ορίζουν ίσως έναν υπότυπο/φαινότυπο με άγχος και κόπωση στον πληθυσμό αυτών των ασθενών, (3) τα φάρμακα και οι ψυχοθεραπείες για την αντιμετώπιση της σχετιζόμενης με την κατάθλιψη κόπωσης θα πρέπει να στοχεύουν παράλληλα και στην αντιμετώπιση των συννοσηρών αγχωδών διαταραχών.

Λέξεις ευρετηρίου: Αγχώδεις διαταραχές, διαταραχή γενικευμένου άγχους, κόπωση, μείζων κατάθλιψη, συννόσηση

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Research article
Ερευνητική εργασία

Mental pain and suicide risk: Application of the greek version of the Mental Pain and the Tolerance of Mental Pain scale

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According to Shneidman's theory, mental pain or "psychache", which refers to an endopsychic painful experience consisted of excessively felt negative feelings, is a key component to the understanding of suicidal behaviour, as to its psychological features. Shneidman himself supported that 'suicide is caused by psychache', more precisely suicide occurs when a person can no longer tolerate this pain. Findings of previous studies have shown that mental pain is an independent predictive factor for suicidal behaviour. In the present study we evaluated the psychometric properties of the Greek version of the Mental Pain Scale (MPS) and the Tolerance for Mental Pain Scale (TMPS) in a non clinical sample consisted of 112 participants (73 female and 39 male). Moreover, we explore the relationships between mental pain, depression, and suicide risk and for the first time the effect of the tolerance for mental pain on depression and suicide risk. We hypothesized that both the level of mental pain and the degree of tolerance for mental pain would predict suicide risk, independently of the level of depression. Both MPS and TMPS appear to have satisfactory to high levels of internal consistency, test-retest reliability, and concurrent validity. Suicide risk was correlated to mental pain, tolerance for mental pain, and depression. Multiple regression analysis showed that mental pain and tolerance for mental pain have a significant contribution to suicide risk, independently of depression, confirming our hypothesis. Using an additional multivariate regression with the factors extracted from MPS and TMPS as independent variables, we found that especially 'loss of control' of mental pain and the ability to 'contain the pain' contribute uniquely to suicide risk. Our findings offer support to the hypothesis that mental pain is a clinical entity distinct from depression with a specific and important contribution to the suicide risk. Depression alone is not enough to cause suicide. The mental pain construct, although related to depression, could shed light on the comprehension of the human experience that leads to suicide. Relieving

mental pain may constitute a distinct and important treatment goal, along with the remission of depression and despair, so that the person can maintain control and contain all the distressing events that comprise the painful experience. Both MPS and TMPS appear to be valid and reliable tools for the assessment of mental pain and its tolerance, respectively. They could also be employed in further investigation on the role of specific aspects of the mental pain experience in suicidal behaviours.

Key words: Mental pain, psychache, suicide risk, tolerance of mental pain, depression

Introduction

There is a substantial body of evidence on the role of stress factors, risk factors, personal vulnerabilities and psychopathology in suicidal behaviour.[1] However, it has been suggested that suicide cannot be understood outside of the long-standing self-destructive processes that generate it.[2,3] According to this theoretical perspective, the focus of research might be the cognitions, emotions and tendencies that deteriorate one's sense of well-being, self-love and life meaning. The concept of mental pain is crucial for understanding how these self-destructive processes eventually lead to suicide.

Definition and evaluation of mental pain

"I can't take the pain anymore...",
"The pain is unbearable..."

The word "pain" is very commonly found in suicide notes; however it is referring to psychological or mental, rather than physical pain.[4] Mental pain has been considered to be an experience even worse than physical pain.[5] Bolger[6] defined emotional pain as a "brokenness of self", which is threatening for a man's identity at both interpersonal and intrapersonal level. Orbach[7] describes mental pain as "an irrevocable sense of hurt and as a perception of negative changes in the self and its functions, accompanied by negative feelings and cognitions".

Edwin Shneidman,[8] the well-renowned suicidologist, was the first to suggest that there is a crucial association between mental pain and suicide. He introduced the term "psychache" to describe an introspective experience with over flooding feelings of "guilt, shame, humiliation or loneliness or fear or angst or dread of growing old or dying badly". According to Shneidman, psychache (or mental pain) is necessary to commit suicide: more precisely, suicide occurs when a person can no longer tolerate this pain. Individuals have certain thresholds for mental pain as well as for physical pain. Thus, from a phenomenological point of view mental pain is the essential endopsychic feature of suicidal behaviour.

Shneidman[9] was also the first to point out the importance of quantification of mental pain for further study on its role in suicide. On the contrary, Leenars[10,11] suggested the idiographic method and specifically the study of suicide notes. Shneidman[9] developed the Psychological Pain Assessment Scale (PPAS), which evaluate mental pain using the projective techniques. The PPAS was found to be sensitive to current suicidal ideation, but not to be related to the history of suicidality.[12] Two other scales have been developed, following Shneidman's suggestions. Holden et al[13] created the 13-item self-rating Scale of Psychache, whereas Orbach et al[2] devised the more extensive Orbach & Mikulincer Mental Pain Scale (MPS), a 45-item self-report instrument measuring various aspects of the painful experience.

Mental pain and suicide

Previous studies on mental pain focused on its distinction from depression, on the one hand, and its relationship with suicide, on the other hand. The correlations of mental pain with suicidal ideation and history of suicidality are consistent findings, thus confirming Shneidman's theory as well as the formulation of the concept of mental pain. "Unbearable psychological pain" was found to be strongly correlated with suicide than other intrapsychic correlates.[10,11] Furthermore, the intensity of mental pain

measured on a numerical scale similar to the one used for physical pain, was found to correlate with the intensity of suicidal ideation in patients with an acute depressive episode.[14] Findings of the same study suggest that mental pain is more intense in both patients who had recently attempted suicide and those who had made a suicidal attempt in the past. Examining mental pain in recent suicide attempters, Levi et al[5] found that it is significantly related to suicidality but not to the seriousness of the attempts.

Studies using the MPS in non-clinical populations showed that, although related to depression and anxiety, mental pain is independently related to suicidality and constitutes a distinct clinical entity – one that cannot be adequately described by means of the existing concepts.[2] In another study using the same scale, "emptiness" as a specific component of mental pain was found to distinguish suicidal patients from non-suicidal ones, irrespectively of the levels of depression, anxiety and hopelessness.[3] Findings of more recent studies also support the hypothesis that mental pain is a predictor of suicidality, moreover an independent of and stronger than depression and hopelessness.[16,17]

There is as yet a lack of evidence on mental pain tolerability, although it is inherent to the notion of mental pain as a feature of suicidal behaviour, since "when the threshold for enduring mental pain is low, suicide risk appears".[7] Shneidman[8] maintained that the most crucial factor for suicide is intolerability, not the intensity of the pain. A preliminary study showed that low levels of tolerance of mental pain were associated with suicide behaviour.[18]

Aims of the study

In the present study we evaluated the psychometric properties (reliability and validity) of the Greek version of the MPS and the TMPS in a non-clinical sample. Moreover, we explore the relationships between mental pain, tolerance for mental pain, depression, and suicide risk. Based on the findings of previous studies, we hypothesized that both the level of mental pain and the degree of tolerance for mental pain would predict suicide risk, independently of the level of depression.

Material and method

Participants

One hundred-twelve participants, 73 female and 39 male, were recruited from the local community. Exclusion criteria for participation in the study were mental retardation, a history of psychosis, currently taking psychiatric medication, and age under 18 or above 65 years. Basic demographic data and information on personal and family psychiatric history were obtained on the day of testing. The male and female groups were matched for age, ethnicity (all Greek) and education level. All participants had been informed about the research procedures and given written informed consent.

Procedure

All participants were asked to complete the following set of questionnaires.

1. *The Orbach & Mikulincer Mental Pain Scale (MPS)[2]*

The MPS is a 45-item self-report questionnaire developed to quantify both the current and the worst ever mental pain. Each item is rated from 1 to 5, with higher scores indicating more painful experience. The scale consists of 9 subscales measuring aspects of the subjective experience of mental pain: (1) irreversibility (the experience of mental pain as irreversible and perpetual), (2) loss of control (experience of uncontrollability, helplessness, and ambiguity), (3) narcissistic wounds (hurt-related feelings, such as vulnerability and rejection), (4) emotional flooding (intense and overwhelming emotional states), (5) freezing (inability to react to the situation), (6) self-estrangement (inability to integrate changes in self-identity), (7) confusion (difficulties in cognitive function related to mental pain experience), (8) emptiness (loss of personal meaning produced by the mental pain), and (9) social distancing (approach-avoidance social orientation during the mental pain experience). MPS demonstrated high internal consistency and test-

retest reliability[2] and strong association with suicidality.[3]

2. The Tolerance for Mental Pain Scale (TMPS)[18]

The TMPS is a 20-item self-rating scale which assesses the ability to tolerate mental pain. This is a 5-point Likert scale (ranging from 1=not true to 5=very true), with higher scores indicating greater tolerance for mental pain. The scale demonstrated good psychometric properties and three subscales derived from the factorial analysis: (1) surfeit of the pain, (2) belief in the ability to cope with the pain, and (3) containing the pain. According to its authors, with the use of TMPS low levels of tolerance of mental pain were found to be a predictor of suicide behaviour.

3. The Beck Depression Inventory (BDI)[19]

The BDI was used to measure depression. This is a 21-item self-report that has been widely used to assess intensity of depression in both psychiatric and normal populations.[20] The Greek version of the scale[21] has been also widely used.

4. The Suicide Risk Scale (SRS)[22]

This is a 15-item self-report scale that measures the risk of suicidal behaviour. A Greek version of the SRS was used in a previous study to assess suicidality in psychiatric patients.[23]

The MPS and the TMPS were translated by the first and the last author from English to Greek. The Greek texts were given to a third bilingual psychologist who blindly translated them back to English. Another bilingual psychologist examined whether the back-translation version successfully conveyed the original English scales.

On the day of testing all participants also completed three visual analogical scales ranging from 0 (none) to 10 (maximum possible degree) which assessed current mental pain, worst ever mental pain, and tolerance for mental pain, and were used to examine the concurrent validity of the MPS –current and worst ever– and the TMPS, respectively. To evaluate the test-retest reliability, the MPS and the TMPS were readministered to one half of the participants (36 female and 20 male) one week after the first administration.

Statistical analysis

Intraclass correlations (ICCs) were used to evaluate test-retest reliability of the MPS and the TMPS as well as their subscales, and Pearson's product moment coefficient r was used to determine inter-item correlations and correlations between each item and the total score minus that item. Cronbach's alpha was estimated in order to examine the internal consistency of the scales and their subscales. The concurrent validity was examined through the Pearson's r values between the MPS and TMPS total scores and the score on the respective visual analogical scales.

Comparisons between male and female groups were made using the independent samples t-test. The correlations between the scales were assessed by the means of Pearson's r coefficient. A multiple regression analysis using step-up criteria was performed to examine the independent contribution of depression, mental pain and tolerance for mental pain to suicide risk. A second hierarchical multiple regression analysis was used to explore the effect of specific aspects of mental pain (MPS and TMPS subscales) on the suicide risk. Statistical analyses were performed using SPSS version 15.0.

Results

Sample Characteristics

The mean age of our study participants was 42.5 (± 12.1) years. The 37.8% of them were unmarried and 11.7% declare unemployed. Twelve subjects (10.8%) reported a personal and 19 (17.1%) a family history of mental disorder (almost exclusively affective or anxiety disorders). Demographic and clinical characteristics of female and male groups are presented in table 1. The groups were found to be well-matched with respect to age and education level. The female group showed significantly higher scores than the male group on the irreversibility and the worst ever subscales of the MPS.

MPS and TMPS reliability and validity

The Cronbach's alpha of the MPS was 0.96, indicating a high level of internal consistency. Correlations

Table 1. Demographic and clinical characteristics of the sample (N=112)

	Female (N=73) Mean (SD)	*Male (N=39) Mean (SD)*	*t*	*p*
Age (years)	42.0 (11.9)	43.4 (12.5)	–0.57	0.566
Education (years)	13.3 (2.7)	13.2 (2.9)	0.18	0.855
BDI	8.7 (6.8)	6.4 (5.4)	1.76	0.081
MPS-total	77.5 (25.2)	70.1 (20.6)	1.53	0.129
1. Irreversibility	16.7 (7.8)	13.6 (5.6)	2.20	0.030
2. Loss of control	16.9 (5.9)	14.8 (5.4)	1.83	0.070
3. Narcissistic wounds	6.4 (2.2)	6.2 (2.5)	0.44	0.661
4. Emotional flooding	9.4 (3.8)	8.6 (6.3)	0.91	0.365
5. Freezing	4.0 (1.8)	3.7 (1.1)	0.91	0.364
6. Self-estrangement	4.9 (1.8)	4.5 (1.6)	1.17	0.243
7. Confusion	5.5 (2.3)	4.7 (2.3)	1.64	0.105
8. Emptiness	4.2 (1.8)	3.8 (1.8)	0.97	0.333
MPS-worst ever	107.2 (44.8)	87.6 (33.6)	2.34	0.021
TMPS-total	68.0 (13.1)	70.4 (13.3)	–0.90	0.370
1. Surfeit of the pain	31.7 (8.7)	33.8 (9.5)	–1.16	0.248
2. Ability to cope with the pain	22.8 (4.5)	22.2 (5.1)	0.66	0.507
3. Containing the pain	13.6 (3.5)	14.5 (3.0)	–1.38	0.170
SRS	3.0 (2.5)	2.2 (1.8)	1.75	0.082

BDI, Beck Depression Inventory; MPS, Mental Pain Scale; TMPS, Tolerance for Mental Pain Scale; SRS, Suicide Risk Scale

coefficients r between the items ranged from 0.27 to 0.86 and between each item and the total score minus that item ranged from 0.19 to 0.74. The Cronbach's alpha of the MPS-worst ever scale was 0.98 and inter-item and item-total correlation coefficients ranged from 0.29 to 0.88 and from 0.19 to 0.82, respectively. Regarding the MPS subscales, the alpha coefficients for the first eight subscales ranged from 0.74 to 0.91, indicating acceptable or high levels of internal consistency. The alpha coefficient of the social distancing subscale was low (0.39) and therefore this subscale was omitted for further data analysis. Of note, previous analyses had also shown low levels of internal consistency for this subscale[15] (also Orbach, personal communication).

The internal reliability levels of the TMPS were found satisfactory. The alpha coefficients were 0.84 for the total scale and 0.87, 0.76, and 0.72 for its three previously mentioned subscales, respectively. Correlations coefficients r between the items ranged from 0.28 to 0.67 and between each item and the total score minus that item ranged from 0.18 to 0.73.

The MPS total score test-retest ICC was 0.92 and ICCs for the eight subscales ranged from 0.83 to 0.95, indicating good test-retest reliability of the scale.

Table 2. Correlations between SRS score and demographic or clinical variables in the total sample (n=112)

	SRS	
	r	*p*
Age (years)	–0.09	0.330
Education (years)	0.10	0.277
BDI	0.61	0.001
MPS-total	0.69	0.001
1. Irreversibility	0.60	0.001
2. Loss of control	0.71	0.001
3. Narcissistic wounds	0.54	0.001
4. Emotional flooding	0.43	0.001
5. Freezing	0.53	0.001
6. Self-estrangement	0.55	0.001
7. Confusion	0.52	0.001
8. Emptiness	0.43	0.001
MPS-worst ever	0.69	0.001
TMPS-total	–0.54	0.001
1. Surfeit of the pain	–0.43	0.001
2. Ability to cope with the pain	–0.31	0.001
3. Containing the pain	–0.52	0.001

BDI, Beck Depression Inventory; MPS, Mental Pain Scale; TMPS, Tolerance for Mental Pain Scale; SRS, Suicide Risk Scale

On the other hand, the social distancing subscale showed week test-retest reliability (ICC=0.41), further supporting its exclusion from the analysis. The MPS-worst ever score test-retest ICC was 0.96. The TMPS

also demonstrated high test-retest reliability. The ICC was 0.95 for the total score and 0.95, 0.92, and 0.92 for the three subscale scores, respectively.

With regards to concurrent validity, both MPS and TMPS showed significant correlations with their respective visual analogical scales. The correlation coefficients were 0.44 (p<0.001), 0.52 (p<0.001), and 0.43 (p<0.001), regarding the participants' MPS-total score, MPS-worst ever score, and TMPS-total score, respectively.

Associations between mental pain, depression and suicide risk

As shown in table 2, the SRS score was significantly correlated with BDI, MPS and TMPS total scores, as well as all the MPS and TMPS subscale scores. The BDI score was significantly correlated with the MPS (r=1, p<0.001) and TMPS (r=0.40, p<0.001) total scores. Correlation between the MPS and the TMPS total score was also significant (r=0.42, p<0.001). Age was positively correlated with the MPS-worst ever scale (r=0.29, p=0.003) and negatively with the emotional flooding subscale of the MPS (r=–0.22, p=0.021). No other clinical variable was significantly correlated either with age or the education level.

A multiple regression model was created using the step-up criteria, with the SRS score as a dependent variable and BDI, MPS, and TMPS total scores as predictors. In the final model obtained, which explained 57% of the variance, the variance level accounted for by all the potential predictors remained significant (see table 3).

Table 3. The effect of mental pain, tolerance for mental pain, and depression on suicide risk calculated using stepwise multiple regression analysis

	*Contribution of each variable at last step**				
Variable	*B*	*SE*	*β*	*t-value*	*p*
MPS-total	0.04	0.01	0.41	4.42	0.001
TMPS-total	0.05	0.01	–0.27	–3.67	0.001
BDI	0.08	0.03	0.23	2.48	0.015

*R^2=0.57, F=13.47, p=0.001
B=the regression coefficient; SE=standard error of B; β=standardized regression co-efficient
Dependent variable: SRS total score
BDI, Beck Depression Inventory; MPS, Mental Pain Scale; TMPS, Tolerance for Mental Pain Scale; SRS, Suicide Risk Scale

In order to explore the independent effect of specific aspects of mental pain on the suicide risk, we created another multiple regression model, in which the independent variables were entered hierarchically in order of the strength of their correlation with SRS score (see table 2). Thus, the MPS and TMPS subscales were entered at the first and the last step of the regression analysis, respectively. As shown in table 4, in the last step, which explained 60% of the variance, only the variance level accounted for by the "loss of control" subscale of MPS and the 'containing the pain' subscale of TMPS remained significant.

Discussion

In the present study we examined the psychometric properties of the Greek version of the Mental Pain and the Tolerance for Mental Pain scales. The MPS was found to have high levels of both internal consistency and test-retest reliability. However, internal consistency and test-retest reliability of the social distancing factor of the scale were unsatisfactory, similarly to the results of a previous study.[15] Thus, this factor appears to be not reliable and was therefore omitted from the further analyses. With the above exception, our findings are consistent with the evaluation of the original scale,[2] which found high levels of test-retest reliability (Pearson's r from 0.79 to 0.94) and internal consistency (Cronbach's alpha from 0.75 to 0.95) of

Table 4. Hierarchical multiple regression analysis to determine the role of mental pain dimensions, aspects of tolerance for mental pain, and depression in suicide risk

	*Contribution of each variable at last step**				
*Variable***	*B*	*SE*	*β*	*t-value*	*p*
Step 1: MPS-subscales					
Loss of control	0.19	0.03	0.49	5.77	0.001
Step 2: BDI	0.07	0.03	0.20	2.22	0.028
Step 3: TMPS-subscales					
Containing the pain	–0.18	0.05	–0.26	–3.61	0.001

*R^2=0.60, F=13.07, p=0.001
**Only variables included in the final model are displayed
B=the regression coefficient; SE=standard error of B; β=standardized regression co-efficient
Dependent variable: SRS total score
BDI, Beck Depression Inventory; MPS, Mental Pain Scale; TMPS, Tolerance for Mental Pain Scale; SRS, Suicide Risk Scale

the individual factors. In our study, TMPS also demonstrated high levels of test-retest reliability and satisfactory internal consistency. Furthermore, with regards to concurrent validity, both scales showed significant correlations with their respective visual analogue scales.

The negative correlation of the emotional flooding factor with the age of the subjects observed in the present study has been also found in the original research. There was no significant correlation between age and irreversibility or confusion factors, which found previously to negatively correlate with age.[2] On the other hand, we found a positive correlation between age and the total score of the worst-ever mental pain. There are as yet no data on the relationship of the worst-ever painful experience with demographic and clinical variables. However, it was to be expected that the possibility of more painful experiences increases with age. The women's higher score in the irreversibility factor and the worst-ever subscale of MPS has not been previously found, although a significant effect for gender on the set of all MPS factors has been reported.[2] This seems to be consistent with the higher levels of depression and the more frequent suicide attempts repeatedly reported in women compared to men.[20,24] Moreover, women had higher, though not significant, scores in both BDI and SRS than men in our sample.

According to available data, there is a strong association between mental pain and depression[2,14,16,17,25,26] while both of them have specific contribution to suicidality.[2,3,8,13–17,27] These complex relationships were replicated by our study using SRS as a measure of suicide risk. In addition, we explore for the first time the effect of the tolerance for mental pain on depression and suicide risk. While the tolerance for mental pain is associated with both the intensity of mental pain experience and the level of depression, it is also a predictive factor for suicide risk independently of these two correlates.

We further examine the contribution of the specific components of mental pain experience and tolerance for mental pain to suicide risk. Loss of control was the only aspect of mental pain experience which had a significant effect on suicide risk, while in a previous study comparing between clinical groups irreversibility and emptiness was also associated with suicidality.[3] The ability of containing the pain was the component of tolerance with a significant effect on the suicide risk. Thus, it appears that the experience of the unbearability and not the intensity or other qualities of pain experience is the key link between the mental pain and sucidality, as predicted by Sneidman[8] and found in previous studies of suicide notes.[10,11]

There are several limitations of this study. A major one is that we did not include a specific measure of hopelessness which has been also found to be a predictive factor for suicidality independently of depression.[3,16,17] Moreover, although our sample-size was sufficient for the evaluation of the psychometric properties of the MPS and the TMPS, was not large enough for a new factorial analysis. Therefore we evaluated the reliability and validity of the factors found by the authors of the scales. Finally, we used an estimation of suicide risk and not a more specific clinical variable, such as the history of suicidal attempts, since our sample was a non-clinical one.

In conclusion, our findings offer support to the hypothesis that mental pain is a clinical entity distinct from depression with a specific and important contribution to the suicide risk. Depression alone is not enough to cause suicide. The mental pain construct, although related to depression, could shed light on the comprehension of the human experience that leads to suicide. Relieving mental pain may constitute a distinct and important treatment goal, along with the remission of depression and despair, so that the person can maintain control and contain all the distressing events that comprise the painful experience. Both MPS and TMPS appear to be valid and reliable tools for the assessment of mental pain and its tolerance, respectively. They could also be employed in further investigation on the role of specific aspects of the mental pain experience in suicidal behaviours.

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Appendix A

Greek version of the Orbach & Mikulincer Mental Pain Scale (MPS)

Κλίμακα Ψυχικού Πόνου

Ο ψυχικός πόνος είναι μια εμπειρία οικεία στον καθένα. Περιγράφει πώς είναι το βίωμα του ανθρώπου όταν αγωνιά και υποφέρει. Θα θέλαμε να μας βοηθήσετε να κατανοήσουμε τι περνούν οι άνθρωποι όταν βιώνουν ψυχικό πόνο. Οι ακόλουθες προτάσεις περιγράφουν διαφορετικές όψεις του ψυχικού πόνου. Θα θέλαμε να μάθουμε ποιες από τις προτάσεις περιγράφουν τη δική σας εμπειρία για τον ψυχικό πόνο στην παρούσα φάση. Να θυμάστε ότι δεν υπάρχει σωστή ή λάθος απάντηση. Το σημαντικό για μας είναι να μάθουμε για την πραγματική προσωπική σας εμπειρία. Κάθε πρόταση πρέπει να βαθμολογηθεί σε μια κλίμακα από το 1 έως το 5.

Αν διαφωνείτε έντονα με την πρόταση, κυκλώστε το 1.

Αν διαφωνείτε με την πρόταση, κυκλώστε το 2.

Αν συμφωνείτε μέχρι ενός σημείου με την πρόταση, κυκλώστε το 3.

Αν συμφωνείτε με την πρόταση, κυκλώστε το 4.

Αν συμφωνείτε έντονα με την πρόταση, τότε κυκλώστε το 5.

	Στην παρούσα στιγμή	*Στη χειρότερη στιγμή*
1. Κανείς δεν ενδιαφέρεται για μένα	1 2 3 4 5	1 2 3 4 5
2. Είμαι εντελώς αβοήθητος	1 2 3 4 5	1 2 3 4 5
3. Νιώθω συναισθηματική αναταραχή μέσα μου	1 2 3 4 5	1 2 3 4 5
4. Δεν μπορώ να κάνω τίποτα απολύτως	1 2 3 4 5	1 2 3 4 5
5. Θα καταρρεύσω	1 2 3 4 5	1 2 3 4 5
6. Φοβάμαι το μέλλον	1 2 3 4 5	1 2 3 4 5
7. Όλοι με απορρίπτουν	1 2 3 4 5	1 2 3 4 5
8. Με πλημμυρίζουν πολλά συναισθήματα	1 2 3 4 5	1 2 3 4 5
9. Νιώθω εντελώς ηττημένος	1 2 3 4 5	1 2 3 4 5
10. Νιώθω ότι έχω χάσει κάτι σημαντικό που δεν θα το ξαναβρώ	1 2 3 4 5	1 2 3 4 5
11. Νιώθω μουδιασμένος και χωρίς ζωή	1 2 3 4 5	1 2 3 4 5
12. Νιώθω εγκαταλελειμμένος και μόνος	1 2 3 4 5	1 2 3 4 5
13. Δεν ασκώ κανέναν έλεγχο στη ζωή μου	1 2 3 4 5	1 2 3 4 5
14. Τα συναισθήματά μου αλλάζουν συνέχεια	1 2 3 4 5	1 2 3 4 5
15. Είμαι ένας ξένος για τον εαυτό μου	1 2 3 4 5	1 2 3 4 5
16. Οι άλλοι με μισούν	1 2 3 4 5	1 2 3 4 5
17. Νιώθω ότι δεν είμαι πια ο παλιός μου εαυτός	1 2 3 4 5	1 2 3 4 5
18. Είμαι ανάξιος	1 2 3 4 5	1 2 3 4 5
19. Νιώθω ότι έχω παραλύσει	1 2 3 4 5	1 2 3 4 5
20. Δεν μπορώ να συγκεντρωθώ	1 2 3 4 5	1 2 3 4 5
21. Δεν έχω εμπιστοσύνη στον εαυτό μου	1 2 3 4 5	1 2 3 4 5
22. Η δύσκολη κατάσταση δεν θ' αλλάξει ποτέ	1 2 3 4 5	1 2 3 4 5
23. Νιώθω σαν να μην είμαι πραγματικός	1 2 3 4 5	1 2 3 4 5
24. Δυσκολεύομαι να σκεφτώ	1 2 3 4 5	1 2 3 4 5
25. Χρειάζομαι την υποστήριξη των άλλων	1 2 3 4 5	1 2 3 4 5
26. Η ζωή μου έχει αλλάξει για πάντα	1 2 3 4 5	1 2 3 4 5
27. Νιώθω μπερδεμένος	1 2 3 4 5	1 2 3 4 5
28. Δεν ελέγχω τι συμβαίνει μέσα μου	1 2 3 4 5	1 2 3 4 5
29. Ο πόνος μου δεν θα φύγει ποτέ	1 2 3 4 5	1 2 3 4 5
30. Νιώθω σαν να έχει τελειώσει η ζωή μου	1 2 3 4 5	1 2 3 4 5

	Στην παρούσα στιγμή	*Στη χειρότερη στιγμή*
31. Δεν έχω ιδέα τι να περιμένω από το μέλλον	1 2 3 4 5	1 2 3 4 5
32. Κάτι στη ζωή μου έχει καταστραφεί για πάντα	1 2 3 4 5	1 2 3 4 5
33. Νιώθω αβεβαιότητα για τη ζωή μου	1 2 3 4 5	1 2 3 4 5
34. Δεν θα είμαι ποτέ ξανά ο ίδιος άνθρωπος	1 2 3 4 5	1 2 3 4 5
35. Έχω έντονα συναισθηματικά σκαμπανεβάσματα	1 2 3 4 5	1 2 3 4 5
36. Δεν ελέγχω καθόλου την κατάσταση	1 2 3 4 5	1 2 3 4 5
37. Θέλω να με αφήσουν μόνο	1 2 3 4 5	1 2 3 4 5
38. Δεν έχω μελλοντικούς στόχους	1 2 3 4 5	1 2 3 4 5
39. Δεν έχω επιθυμίες	1 2 3 4 5	1 2 3 4 5
40. Δεν έχω διάθεση να μιλάω σε άλλους	1 2 3 4 5	1 2 3 4 5
41. Δεν βρίσκω νόημα στη ζωή μου	1 2 3 4 5	1 2 3 4 5
42. Νιώθω ότι δεν μπορώ να είμαι μόνος	1 2 3 4 5	1 2 3 4 5
43. Δεν μπορώ ν' αλλάξω αυτό που μου συμβαίνει	1 2 3 4 5	1 2 3 4 5
44. Ο πόνος δεν θα φύγει ποτέ	1 2 3 4 5	1 2 3 4 5
45. Νιώθω κενός μέσα μου	1 2 3 4 5	1 2 3 4 5

Appendix B

Greek version of the Tolerance for Mental Pain Scale (TMPS)

Κλίμακα Ανοχής του Ψυχικού Πόνου

Οι παρακάτω προτάσεις σχετίζονται με τον βαθμό που μπορείτε να ανεχθείτε τον ψυχικό πόνο. Παρακαλούμε διαβάστε τες και απαντήστε σε ποιο βαθμό σας εκφράζουν κυκλώνοντας τον αντίστοιχο αριθμό, π.χ. από το *1=δεν είναι αλήθεια* μέχρι το *5=είναι πολύ αλήθεια*. Δεν υπάρχουν σωστές ή λάθος απαντήσεις.

Όταν νιώθω ψυχικό πόνο...

1. Πιστεύω ότι ο πόνος μου θα περάσει	1 2 3 4 5
2. Πιστεύω ότι δεν μπορώ να κάνω τίποτα για να μειώσω τον πόνο μου	1 2 3 4 5
3. Νιώθω ότι ο πόνος μου διακόπτει ό,τι κάνω	1 2 3 4 5
4. Δεν μπορώ να συγκεντρωθώ εξαιτίας του πόνου	1 2 3 4 5
5. Ο πόνος με κατακλύζει τελείως	1 2 3 4 5
6. Αντιμετωπίζω τον πόνο παρότι είναι δύσκολο να τον αντέξω	1 2 3 4 5
7. Υποφέρω πάρα πολύ	1 2 3 4 5
8. Πιστεύω ότι με τον χρόνο ο πόνος θα εξαφανιστεί	1 2 3 4 5
9. Δεν μπορώ να συγκρατήσω τον πόνο μέσα μου	1 2 3 4 5
10. Όταν νιώθω πόνο δυσκολεύομαι να κάνω πράγματα που συνήθως ευχαριστιέμαι	1 2 3 4 5
11. Πιστεύω πως αν κάνω το σωστό, ο πόνος θα εξαφανιστεί	1 2 3 4 5
12. Δεν μπορώ να βγάλω τον πόνο απ' το μυαλό μου	1 2 3 4 5
13. Νιώθω ότι πρέπει να ξεφορτωθώ τον πόνο αμέσως	1 2 3 4 5
14. Ο ψυχικός πόνος που αισθάνομαι μοιάζει καμιά φορά με τον έντονο σωματικό πόνο	1 2 3 4 5
15. Ο πόνος είναι πολύ έντονος	1 2 3 4 5
16. Παρότι είναι δύσκολο ν' αντέξω τον πόνο, ξέρω ότι θα μου περάσει	1 2 3 4 5
17. Πιστεύω ότι θα βρω έναν τρόπο να μειώσω τον πόνο	1 2 3 4 5
18. Ο χρόνος περνάει πολύ αργά όταν νιώθω πόνο	1 2 3 4 5
19. Ο πόνος είναι υπερβολικός για μένα	1 2 3 4 5
20. Σκέφτομαι τον πόνο όλη την ώρα	1 2 3 4 5

Ψυχικός πόνος και κίνδυνος αυτοκτονίας: Εφαρμογή της ελληνικής εκδοχής των κλιμάκων Ψυχικού Πόνου και Ανοχής στον Ψυχικό Πόνο

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Ο ψυχικός πόνος είναι μια εσωτερική επώδυνη ψυχολογική εμπειρία και αναφέρεται στη βίωση υπερβολικά έντονα αρνητικών συναισθημάτων που ματαιώνουν τις ζωτικές ανάγκες του ανθρώπου. Σύμφωνα με τη θεωρία του Shneidman για τη φαινομενολογία της αυτοκτονίας, ο ψυχικός πόνος αποτελεί όχι μόνο τον πιο σημαντικό από τους ψυχολογικούς παράγοντες που σχετίζονται με την αυτοκτονία, αλλά συνιστά την προϋπόθεση σε ψυχολογικό επίπεδο για να επιχειρηθεί η αυτοκτονία. Οι σχετικές μελέτες επιβεβαιώνουν τον ρόλο του ψυχικού πόνου ως ανεξάρτητου προβλεπτικού παράγοντα στην αυτοκτονία, και μάλιστα πιο ισχυρού από την κατάθλιψη. Στην παρούσα μελέτη εκτιμήσαμε τις ψυχομετρικές ιδιότητες της ελληνικής εκδοχής της Κλίμακας Ψυχικού Πόνου (ΚΨΠ) καθώς και της Κλίμακας Ανοχής στον Ψυχικό Πόνο (ΚΑΨΠ) χορηγώντας τις σε μη κλινικό δείγμα αποτελούμενο από 112 συμμετέχοντες (73 γυναίκες και 39 άνδρες). Επιπλέον εξετάσαμε τη συσχέτιση του ψυχικού πόνου, της ανοχής στον ψυχικό πόνο και της κατάθλιψης με τον κίνδυνο αυτοκτονίας. Υποθέσαμε ότι τόσο το επίπεδο του ψυχικού πόνου όσο και της ανοχής στον ψυχικό πόνο θα λειτουργούν προβλεπτικά για την αυτοκτονικότητα, ανεξάρτητα από την κατάθλιψη. Αμφότερες οι κλίμακες έδειξαν από ικανοποιητικά ως υψηλά επίπεδα αξιοπιστίας κι εγκυρότητας, σε συμφωνία και με την αρχική μελέτη για τις ψυχομετρικές ιδιότητές τους, με εξαίρεση ενός από τους παράγοντες της ΚΨΠ. Ο ψυχικός πόνος συσχετίστηκε σημαντικά με τον αυτοκτονικό κίνδυνο, αλλά και με την κατάθλιψη, επιβεβαιώνοντας ευρήματα προηγούμενων μελετών. Ο ψυχικός πόνος και η καταθλιπτική συμπτωματολογία βρέθηκε ότι έχουν ανεξάρτητη συμβολή στον αυτοκτονικό κίνδυνο. Επιπλέον, η ανοχή του ψυχικού πόνου βρέθηκε επίσης να συμβάλλει στον αυτοκτονικό κίνδυνο, ανεξάρτητα από την κατάθλιψη και τον ψυχικό πόνο, παρότι σχετίζεται με τις μεταβλητές αυτές. Εξετάσαμε ακόμη την ξεχωριστή συνεισφορά στον αυτοκτονικό κίνδυνο των επιμέρους παραγόντων του ψυχικού πόνου και της ανοχής σε αυτόν. Η απώλεια του ελέγχου κατά τη βίωση του ψυχικού πόνου καθώς και η δυνατότητα να εμπεριέχει κανείς τον πόνο ως παράγοντας ανοχής στον ψυχικό πόνο, βρέθηκε ότι έχουν τη μεγαλύτερη επίδραση στον αυτοκτονικό κίνδυνο. Προκύπτουν συνεπώς στοιχεία υπέρ της υπόθεσης του Shneidman ότι η έννοια της ανοχής στον ψυχικό πόνο αποτελεί κλειδί στην κατανόηση της εμπειρίας αυτής και στη σχέση της με τον αυτοκτονικό κίνδυνο. Τα ευρήματά μας επιβεβαιώνουν επίσης την αρχική μας υπόθεση σχετικά με τον σημαντικό ρόλο του ψυχικού πόνου στην αυτοκτονία, καθώς και το ότι αποτελεί ξεχωριστή κατασκευή από την κατάθλιψη. Κατά προέκταση αναδεικνύεται και η σημασία του ψυχικού πόνου ως θεραπευτικού στόχου, πέρα από την καταθλιπτική συμπτωματολογία, για την πρόληψη της αυτοκτονίας. Τόσο η ΚΨΠ, όσο και η ΚΑΨΠ αποτελούν έγκυρα κι αξιόπιστα εργαλεία εκτίμησης της εμπειρίας του ψυχικού πόνου και της ανοχής σε αυτόν, χρήσιμα στην κλινική πράξη.

Λέξεις ευρετηρίου: Ψυχικός πόνος, κίνδυνος αυτοκτονίας, ανοχή στον ψυχικό πόνο, κατάθλιψη

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  Οργαν. Γραφείο: Κοινωνικός Συνεταιρισμός Περιορισμένης Ευθύνης Κοι.Σ.Π.Ε. Ν. Αχαΐας «ΦΑΡΟΣ»
  κ. Καραγεωργοπούλου Ειρήνη
  Τηλ.: 2610 362 949
  E-mail: koispeachaias@yahoo.gr
- **"7th European Congress on Violence in Clinical Psychiatry "Challenges for care and treatment", Prague, Czech Republic**
  19–22 October, 2011
  Contact: Mr. N.E. Oud
  Organizers: European Violence in Psychiatry Research Group, Oud Consultancy and Conference Management
  Collaboration: WPA Section on Art and Psychiatry, Czech Psychiatric Association
  E-mails: nico.oud@freeler.nl, conference.management@freeler.nl
  Websites: www.oudconsultancy.nl, www.oudconsultancy.nl/prague_cfa/index.html
- **"5th International Congress on Brain & Behaviour", The Met Hotel, Thessaloniki, Greece**
  3–6 November, 2011
  Contact: Prof G. Kaprinis, Prof K. Fokas
  Congress Secretariat: Triaena Tours & Congress S.A., Sakellaridi 25, 54248 Thessaloniki, Greece
  Tel.: +30-2310256194-5, Fax: +30-2310256196
  E-mail: isbb@triaenatours.gr
- **"WPA Regional Meeting", Taipei, Taiwan**
  12–13 November, 2011
  Organizer: Taiwanese Society of Psychiatry
  Contact: Dr Chiao-Chicy Che,
  E-mail: twpsyc@ms61.hinet.net
- **2nd International Congress on Neurobiology, Psychopharmacology & Treatment guidance, Thessaloniki, Greece**
  24–27 November, 2001
  Contact: Ast. Prof. Konstantinos N. Fountoulakis
  Congress Secretariat: Global Events,
  50A Stadiou Str 55535 Pylea,
  Thessaloniki, Greece
  Tel: +30-2310 247734-43, Fax: +30-2310 247746
  E-mail: info@globalevents.gr
  Website: www.globalevents.gr
- **1ο Εκπαιδευτικό Σεμινάριο «Περιγεννητική Ψυχιατρική», Αθήνα**
  9 Δεκεμβρίου 2011
  Οργ. Φορέας: Περιοδικό «Ψυχιατρική» ΕΨΕ
  Συνεργασία: ΕΚΠΑ
  Επικοινωνία: Καθ. Β. Κονταξάκης, Αναπλ. Καθ. Ι. Ζέρβας
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  E-mail: editor@psych.gr
- **2ο Εκπαιδευτικό Σεμινάριο «Η Κοινοτική Ψυχιατρική σήμερα», Αθήνα**
  13 Ιανουαρίου 2012
  Οργ. Φορέας: Περιοδικό «Ψυχιατρική» ΕΨΕ
  Συνεργασία: ΕΚΠΑ
  Επικοινωνία: Καθ. Β. Κονταξάκης,
  Αναπλ. Καθ. Δ. Πλουμπίδης
  Τηλ.: 210-7758410, 6942950257, 6944189393,
  Fax: 210-7758405
  E-mail: editor@psych.gr

- **WPA Thematic Conference-Community Psychiatry and Family Medicine**
  Joint Promotion of Mental Health Care, Granada, Spain
  9–11 February, 2012
  Organizer: (a) World Psychiatric Association, (b) Spanish Association of Neuropsychiatry
  Collaboration: (a) WONCA International and WONCA Europe, (b) University of Granada
  Contact: Dr Fransisco Torres, E-mail: ftorres@ugr.es

- **3ο Εκπαιδευτικό Σεμινάριο «Επείγουσα Ψυχιατρική», Αθήνα**
  10 Φεβρουαρίου 2012
  Οργ. Φορέας: Περιοδικό «Ψυχιατρική» ΕΨΕ
  Συνεργασία: ΕΚΠΑ
  Επικοινωνία: Καθ. Β. Κονταξάκης, Επικ. Καθ. Μ. Μαργαρίτη
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- **4ο Εκπαιδευτικό Σεμινάριο «Η κατάθλιψη σήμερα: θέματα διάγνωσης-έκβασης και ψυχομετρικές εκτιμήσεις», Αθήνα**
  2 Μαρτίου 2012
  Οργ. Φορέας: Περιοδικό «Ψυχιατρική» ΕΨΕ
  Συνεργασία: ΕΚΠΑ
  Επικοινωνία: Καθ. Β. Κονταξάκης, Επικ. Καθ. Μ. Χαβάκη-Κονταξάκη
  Τηλ.: 210-7289257

- **4ο Εκπαιδευτικό Σεμινάριο «Η Κατάθλιψη σήμερα: Θέματα διάγνωσης – έκβασης και ψυχομετρικές εκτιμήσεις», Αθήνα**
  2 Μαρτίου 2012
  Οργ. Φορέας: Περιοδικό «Ψυχιατρική», ΕΨΕ
  Συνεργασία: ΕΚΠΑ
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- "**Mental Disorders and Urbanization: Challenges of Societies in Transformation", São Paulo, Brazil**
  14–17 March, 2012
  Contact: Bia Adler
  Organizer: University of São Paulo, Department and Institute of Psychiatry, Section of Psychiatric Epidemiology
  Collaboration: Paris Descartes University, University College London
  E-mail: bia.adler@gmail.com
  Website: https: //wpaepi2012brazil.com

- **2ο Συνέδριο Βιοψυχοκοινωνικής Προσέγγισης στην Ιατρική περίθαλψη, The Met Hotel, Θεσσαλονίκη**
  15–17 Μαρτίου 2012
  Οργ. Φορέας: Γ' Ψυχιατρική Κλινική ΑΠΘ
  Επικοινωνία: Καθ. Α. Ιακωβίδης
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  Τηλ.: +30 2310 460682, 2310 469652, Fax: +30 2310 435064
  E-mail: info@praxicon.gr
  Website: www.praxicon.gr

- **ECNP Workshop on Neuropsychopharmacology for young scientists in Europe, Lyou, France**
  15–18 March 2012
  Organizer: European College of Neuropharmacology (ECNP)
  Contact: ECNP Office
  Tel: +31302538567
  E-mail: nice2012@ecupeu
  Website: www.ecnp.eu

- **5ο Εκπαιδευτικό Σεμινάριο «Περιγεννητική ψυχιατρική ΙΙ: Ψυχολογία και ψυχοθεραπεία», Αθήνα**
  30 Μαρτίου 2012
  Οργ. Φορέας: Περιοδικό «Ψυχιατρική», ΕΨΕ
  Συνεργασία: ΕΚΠΑ
  Επικοινωνία: Καθ. Β. Κονταξάκης, Αναπλ. Καθ. Ι. Ζέρβας
  Τηλ.: 210-7758410, 6942950257, 6974701145,
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  E-mail: editor@psych.gr

- **Επιστημονική Ημερίδα «Σχολεία..... ζώντας την εφηβεία», Αμφιθέατρο ΠΓΝ, Πάτρα**
  30 Μαρτίου 2012
  Οργάνωση: Ψυχιατρική Κλινική Πανεπιστημίου Πατρών
  Επικοινωνία: Αναπλ. Καθ. Φ. Γουρζής
  Τηλ.: 2610990559, 6976602460, Fax: 2610994534
  E-mail: pgourzis@upatras.gr

- **WPA Thematic Conference: Addiction Psychiatry, Barcelona, Spain**
  29–31 March, 2012
  Organizer: Socidrogalcohol
  Contact: Julio Bobes Garcia
  E-mail: (a) bobes@ctv.es, (b) bobes@uniovi.es

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

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

- **25η Πανελλήνια Εκπαιδευτική Διημερίδα Ειδικευομένων Ψυχιάτρων, Κυλλήνη Αχαΐας**
  11–13 Μαΐου 2012
  Οργάνωση: (α) Ελληνική Ψυχιατρική Εταιρεία (ΕΨΕ)
  (β) Ένωση Ελλήνων Ειδικευομένων Ψυχιάτρων (ΕΕΕΨ)

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Τηλ.: 210-7758410, 6942950257, 6974715296,
Fax: 210-7758405
E-mail: editor@psych.gr

- **«Σύγκρουση και συμφιλίωση: Στις ομάδες, στα ζεύγη, στις οικογένειες, στην κοινωνία», Αθήνα**
  24–27 Μαΐου 2012
  Οργάνωση: (α) Ευρωπαϊκή Ομοσπονδία Ψυχαναλυτικής Ψυχοθεραπείας (ΕΟΨΨ)
  (β) Ελληνική Εταιρεία Ομαδικής Ανάλυσης & Οικογενειακής Θεραπείας
  Οργ. Γραφείο: Easy Travel, Τηλ.: 210-3615201,
  Fax: 210-3625572
  E-mail: secretariat@efppathens2012.gr
- **1st Istanbul- Eurasian Regional Congress of Biological Psychiatry, Instanbul, Turkey**
  27–31 May 2012
  Organizers: Turkish Society of Biological Psychiatry
  Contact: Prof Bilgen Taneli
  Website: www.biologicalpsychiatry-instanbul2012.org
- **"WPA Regional Meeting", Tehran, Iran**
  31 May–2 June, 2012
  Contact: Dr Ahmed Jalili
  Organizer: Iranian Psychiatric Association
  E-mails: info@psychiatrist.ir, sajalili@gmail.com
  Website: www.psychiatrist.ir
- **4ο Πανελλήνιο Ψυχιατρικό Συνέδριο στην Πρωτοβάθμια Φροντίδα Υγείας, Κυλλήνη Ηλείας**
  1–4 Ιουνίου 2012
  Οργάνωση: Ψυχιατρική Κλινική Πανεπιστημίου Πατρών
  Επικοινωνία: Αναπλ. Καθ. Φ. Γουρζής
  Τηλ.: 2610990559, 6976602460, Fax: 2610994534
  E-mail: pgourzis@upatras.gr
- **8ο Διεθνές Ψυχαναλυτικό Συμπόσιο Δελφών, Δελφοί Ελλάς**
  1–4 Ιουνίου, 2012
  Θέμα: «Ο πατέρας»
  Οργ. Γραφείο: Easy Travel
  Αναγνωστοπούλου 19, 106 73 Αθήνα
  Τηλ.: 210-36 15 201, 210-36 09 442, Fax: 210-36 25 572
  E-mail: easytravel@hol.gr
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  Ψυχιατρική Κλινική Πανεπιστημίου Πατρών, 265 04
  Ρίο, Πάτρα
  Τηλ.: 2610-992996, Fax: 2610-994534
  E-mail: evouga@upatras.gr
- **"Strategies for Responding to Psychiatric Challenges" Moscow, Russia**
  28 June–1 July 2012
  Organizers: (a) Russian Society of Psychiatrists (RSP)
  (b) International Society of Quality Medicine (ISoQM)
  Organizing Secretariat: Global Events Ltd
  50A Stadiou Str, Pylea 55535
  Thessaloniki, Greece
  Tel: +302310313631, Fax:+302310247746
  Website: www.globalevents.gr
- **25th ECNP Congress, Vienna, Austria**
  13–17 October 2012
  Organizer: European College of Neuropharmacology (ECNP)
  Contact: ECNP Office
  Tel: +31302538567
  E-mail: nice2012@ecupeu
  Website: www.ecnp.eu
- **"WPA International Congress", Prague, Czech Republic**
  17–21 October, 2012
  Contact: Dr Jiri Raboch
  Organizer: Czech Psychiatric Association
  E-mail: wpaic2012@guarant.cz
  Websitewww.wpaic2012.org
- **WPA Regional Congress "Facilitating Mental Health, Primary Care and Public Health Integration", Bucharest, Romania**
  10–13 April 2013,
  Contact: Prof Eliot Sorel
  Tel: +40212105814, Fax: +40212122702
  E-mail: secretariat@wpa2013bucharest.org
  Website: www.wpa2013bucharest.org
- **3rd Congress on Neurobiology, Psychopharmacology and Treatment Guidance, Thessaloniki, Greece**
  30 May–2 June 2013,
  Organizer: International Society of Neurobiology & Psychopharmacology
  Contact: Ast. Prof. K. N. Fountoulakis
  Organizing Secretariat: Global Events Ltd
  Tel: +302310313631, Fax:+302310247746
  Website: www.globalevents.gr
- **WPA Third Thematic Conference on Legal and Forensic Psychiatry, Madrid, Spain**
  12–14 June, 2013
  Organizer: Spanish Society of Legal Psychiatry
  Contact: Dr Alfredo Calcedo Barba
  E-mail: alfredocalcedo@gmail.com
- **26th ECNP Congress, Barcelona, Spain**
  5–9 October 2013
  Organizer: European College of Neuropharmacology (ECNP)
  Contact: ECNP Office
  Tel: +31302538567
  E-mail: nice2012@ecupeu
  Website: www.ecnp.eu

""PSYCHIATRIKI"

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Apart from the printed edition, the journal is freely available in electronic version at the websites: www.psych.gr or www.betamedarts.gr

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1. **Editorials:** Short articles in both English and Greek language covering topics of particular importance, written by members of the Editorial Board or by members of International Advisory Board and by invited authors (up to 500 words and 5–7 references).
2. **Review articles:** Should be written by one or two authors. They should not exceed 7,500 words.
3. **Research papers:** These articles must be based on a research protocol. Statistical evaluation of the findings is essential. They should not exceed 3,000 words.
4. **Brief communications:** This section includes research reports which can be accommodated in a small space. They should not exceed 1,500 words.
5. **Special articles:** Invited articles concerning topics of special interest (up to 6,000 words).
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Hellenic Psychiatric Association,
17, Dionisiou Eginitou str., GR-115 28 Athens, Greece
e-mail: editor@psych.gr

The original manuscript, three copies as well as a copy on a diskette or an electronic copy by e-mail should be submitted. The text must be written with a word processor compatible with any Windows program, or with any program for a Macintosh computer.

The submitted manuscripts should be accompanied by the "Submission form" accurately filled in. Submission form can be found in every issue of the journal.

A code number to be used in further correspondence will be assigned to all papers submitted. Manuscripts should be typewritten, double-spaced on one side of the paper with a margin of at least 3.5 cm. On the right upper corner of the first page a characterization on the article should appear (e.g., Brief Communication, Research Article).

ARRANGEMENT

All pages must be numbered, starting with the title page.

Title page: It indicates the title (which should not exceed 12 words), the names and surnames of the authors, the Institute, Hospital, University, etc. where the work was conducted and the address, telephone number and e-mail of the author who will be responsible for the correspondence. In the same page appreciation for those who have contributed to the presented work can also be included.

Abstract: The second page must include an informative abstract (400–500 words) as well as 4–6 key words.

Main part: Must be divided in sections (e.g., for the Research Papers: Introduction, Material and method, Results, Discussion). Results appearing in the tables should not be reported again in detail in the text.

References: They must be identified in the text by arabic numbers (in brackets) and must be numbered in the order in which they are first mentioned in the text (Vancouver system), e.g. *Birley*[1] *found that... but Alford*[2] *disagreed*. Cite the names of all authors. The list of references should include only those publications which are cited in the text.

References should not exceed 100 in the Review articles and the Special articles, 50 in the General articles, 15 in the Brief Communications and in Case reports, and 8 in the Editorials and the Letters to the Editor.

The following paradigms illustrate the various reference categories:

1. Birley JLT, Adear P, Singer D, Rosenberg M. Electrogastrographic studies in elderly patients. *Gastroenterology* 1980, 79:311–314 (Journal Article).
2. Alford J, Nemiah J. Peptic ulcer in childhood. In: Sodeman WA (ed) *Pathologic Physiology*. Saunders, Philadelphia, 1970:457–472 (Chapter in Book).
3. Kinden A. *Stress and emotion*. Springer, Berlin, 1990 (Book).
4. Larsen E, Elliot B. Fatigue in major depression. *Psychiatriki* 2007, (Suppl 1):S143–S144 (Journal Supplement)
5. Silverstone A, Leman H, Stark J. *Attempted suicide by drug-overdose*. Paper presented at 2nd Congress on Suicide behaviour, 4–6 May 2002, Rome, Abstracts Book, pp 212–213 (Conference Presentation - Abstract Book)
6. Henry A, Andrews B. *Critical issues for parents with mental illness*. N.Y. Centre for Mental Health Services 2001 (Cited 2 June 2005) Available from www. mentalorg/publications (Website)

Abbreviations of journals should conform to the style used in *Index Medicus;* journals not indexed there should not be abbreviated.

Tables: They must appear in a separate page, double-spaced. They must be numbered in the order in which they are mentioned on the text, with arabic numbers (table 1). A descriptive concise title should be included. Avoid vertical lines.

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ΨΥΧΙΑΤΡΙΚΗ"

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Εκτός από την έντυπη έκδοσή του, το περιοδικό διατίθεται ελεύθερα στην ηλεκτρονική του έκδοση από τις ιστοσελίδες: www.psych.gr ή www.betamedarts.gr

Το περιοδικό "ΨΥΧΙΑΤΡΙΚΗ" δέχεται προς δημοσίευση εργασίες που αφορούν πρωτότυπο υλικό που δεν έχει δημοσιευθεί προηγουμένως (εκτός σε μορφή περίληψης) ή δεν έχει υποβληθεί για δημοσίευση κάπου αλλού.

Κατά την υποβολή της εργασίας όλοι οι συγγραφείς πρέπει να υπογράψουν στο τυποποιημένο έντυπο υποβολής (που βρίσκεται συνημμένο σε κάθε τεύχος του περιοδικού) ότι συμφωνούν με το περιεχόμενο και αποδέχονται την υποβαλλόμενη προς δημοσίευση εργασία και μεταβιβάζουν τα συγγραφικά δικαιώματα στο περιοδικό "ΨΥΧΙΑΤΡΙΚΗ". Οι συγγραφείς ακόμη, δηλώνουν ότι: (α) δεν υπήρξε οικονομική υποστήριξη από διάφορες πηγές (εάν υπήρξε πρέπει να δηλωθεί), (β) δεν υπήρξαν αντικρουόμενα συμφέροντα σχετικά με το υλικό της έρευνας που υπεβλήθη προς δημοσίευση, (γ) το πρωτόκολλο της έρευνας εγκρίθηκε από την Επιτροπή Βιοηθικής του Νοσοκομείου ή του Ιδρύματος όπου πραγματοποιήθηκε η έρευνα σύμφωνα με τις προδιαγραφές της Διακήρυξης του Ελσίνκι (1995) όπως αναθεωρήθηκαν στο Εδιμβούργο (2000) και (δ) ότι όλοι οι ασθενείς έδωσαν τη συγκατάθεσή τους πριν συμπεριληφθούν στην έρευνα αφού προηγουμένως ενημερώθηκαν για την ερευνητική διαδικασία.

Τα κριτήρια αποδοχής των εργασιών περιλαμβάνουν την ποιότητα και την πρωτοτυπία της έρευνας, όπως επίσης τη σημαντικότητα και χρησιμότητα των δεδομένων στους αναγνώστες του περιοδικού.

Όλες οι εργασίες υπόκεινται σε μια αρχική εκτίμηση από τον Εκδότη ή μέλη της Συντακτικής Επιτροπής του περιοδικού προκειμένου να εκτιμηθεί η καταλληλότητα και η ποιότητά τους. Εάν η εργασία κριθεί καταρχήν κατάλληλη για δημοσίευση στο περιοδικό, εκτιμάται από δύο ανεξάρτητους κριτές, ειδικούς στο αντικείμενο της έρευνας. Οι κριτές δεν γνωρίζουν τους συγγραφείς της εργασίας και παραμένουν ανώνυμοι για τους συγγραφείς.

Τα σχόλια των κριτών μαζί με τις υποδείξεις και διορθώσεις τους αποστέλλονται στους συγγραφείς. Οι συγγραφείς ενημερώνονται εγγράφως για την τελική απόφαση της Συντακτικής Επιτροπής του περιοδικού όταν η διαδικασία αξιολόγησης ολοκληρωθεί. Τα ονόματα των κριτών του προηγούμενου έτους εμφανίζονται στο πρώτο τεύχος του επομένου έτους. Η Συντακτική Επιτροπή διατηρεί το δικαίωμα να κάνει φραστικές διορθώσεις στα κείμενα προκειμένου να μειώσει ασάφειες και επαναλήψεις και να βελτιώσει τη δυνατότητα επικοινωνίας ανάμεσα στους συγγραφείς και τους αναγνώστες του περιοδικού.

Το περιοδικό «ΨΥΧΙΑΤΡΙΚΗ» καταχωρείται και περιλαμβάνεται στα MEDLINE/PubMed, Index Copernicus, Google Scholar, EMBASE/Excerpta Medica, GFMER, CIRRIE, SCIRUS for Scientific Inf. και στο Iatrotek

ΕΙΔΗ ΑΡΘΡΩΝ

1. **Άρθρα Σύνταξης**: Σύντομα άρθρα γραμμένα ταυτόχρονα στην ελληνική και αγγλική γλώσσα που αναφέρονται σε επίκαιρα θέματα ιδιαίτερης σημασίας. Γράφονται από τη Συντακτική Επιτροπή ή από μέλη της Διεθνούς Συμβουλευτικής Επιτροπής ή μετά από πρόσκληση της Συντακτικής Επιτροπής (μέχρι 500 λέξεις και 5–7 βιβλιογραφικές αναφορές).
2. **Ανασκοπήσεις:** Ενημερωτικά άρθρα που αφορούν σε κριτική ανάλυση ψυχιατρικών θεμάτων ή θεμάτων συγγενών προς την Ψυχιατρική Επιστήμη. Οι ανασκοπήσεις γράφονται από έναν ή δύο συγγραφείς. Η έκτασή τους δεν πρέπει να υπερβαίνει τις 7.500 λέξεις (25 δακτυλογραφημένες σελίδες, διπλό διάστημα γραφομηχανής).
3. **Ερευνητικές εργασίες:** Προοπτικές ή αναδρομικές εργασίες που βασίζονται σε ερευνητικό πρωτόκολλο. Πρέπει οπωσδήποτε να έχει γίνει στατιστική επεξεργασία των αποτελεσμάτων. Οι ερευνητικές εργασίες δεν πρέπει να υπερβαίνουν τις 3.000 λέξεις (10 δακτυλογραφημένες σελίδες, διπλό διάστημα γραφομηχανής).
4. **Σύντομα άρθρα:** Στην κατηγορία αυτή υπάγονται ερευνητικές εργασίες που μπορούν να καταχωρηθούν σε περιορισμένο χώρο. Η έκταση των άρθρων αυτών δεν πρέπει να υπερβαίνει τις 1.500 λέξεις (5 δακτυλογραφημένες σελίδες, διπλό διάστημα γραφομηχανής).
5. **Ειδικά άρθρα:** Γράφονται μετά από πρόσκληση της Συντακτικής Επιτροπής και αναφέρονται σε θέματα, με τα οποία έχει ιδιαίτερα ασχοληθεί ο συγγραφέας π.χ. θεραπεία συμπεριφοράς, παθολογική ζηλοτυπία, ψυχοθεραπεία μεταιχμιακών καταστάσεων (μέχρι 6.000 λέξεις).
6. **Ενδιαφέρουσες περιπτώσεις:** Η κατηγορία αυτή περιλαμβάνει ενδιαφέρουσες αναφορές περιπτώσεων και περιγραφές περιπτώσεων όπου εφαρμόσθηκαν νέες διαγνωστικές ή/και θεραπευτικές μέθοδοι (μέχρι 1500 λέξεις).
7. **Γενικά άρθρα:** Η *ΨΥΧΙΑΤΡΙΚΗ* δέχεται και άρθρα που εκφράζουν θεωρητικές απόψεις στον χώρο της Ψυχιατρικής, γνώμες για τα συστήματα παροχής ψυχιατρικής περίθαλψης, απόψεις για τους χώρους επαλληλίας μεταξύ Ψυχιατρικής και άλλων επιστημών και άλλα άρθρα ανάλογου περιεχομένου. Τα άρθρα αυτά δεν πρέπει να υπερβαίνουν τις 2.000 λέξεις (περίπου 7 δακτυλογραφημένες σελίδες). Η Συντακτική Επιτροπή μπορεί να προτείνει τη συντόμευση των άρθρων αυτών προκειμένου να δημοσιευθούν ως «Επιστολές προς τη Σύνταξη».
8. **Επιστολές προς τη Σύνταξη:** Περιλαμβάνουν σχόλια και κρίσεις πάνω σε ήδη δημοσιευμένες εργασίες, παρατηρήσεις σε επίκαιρα ψυχιατρικά θέματα, πρόδρομα ερευνητικά αποτελέσματα, κ.λπ. Δεν πρέπει να υπερβαίνουν τις 400 λέξεις (συνοδεύεται από σύντομη Αγγλική περίληψη).
9. **Βιβλιοκριτική:** Η παρουσίαση και κριτική βιβλίων γίνεται μετά από πρόσκληση της Συντακτικής Επιτροπής (μέχρι 600 λέξεις - συνοδεύεται από σύντομη αγγλική περίληψη).
10. **Άρθρα στην αγγλική γλώσσα:** Η *ΨΥΧΙΑΤΡΙΚΗ* θα κυκλοφορεί στην Ελληνική γλώσσα πάντα με Αγγλική περίληψη των εργασιών. Ένα ή δύο τεύχη ετησίως θα κυκλοφορούν εξ ολοκλήρου στην Αγγλική (με εκτεταμένη ελληνική περίληψη, 400–500 λέξεις). Στα τεύχη αυτά θα δημοσιεύονται εργασίες ξένων συναδέλφων, αλλά και Ελλήνων. Οι εργασίες Ελλήνων συναδέλφων μπορούν να υποβάλλονται στην Ελληνική ή την Αγγλική γλώσσα. Όσες εργασίες προκρίνονται για δημοσίευση και έχουν υποβληθεί στην Ελληνική γλώσσα θα μεταφράζονται μετά από συνεργασία του περιοδικού με τους συγγραφείς.

ΥΠΟΒΟΛΗ ΕΡΓΑΣΙΩΝ

Οι εργασίες υποβάλλονται στο πρωτότυπο και σε τρία φωτοαντίγραφα, στη διεύθυνση:

Περιοδικό ΨΥΧΙΑΤΡΙΚΗ
Ελληνική Ψυχιατρική Εταιρεία,
Διονυσίου Αιγινήτου 17, 115 28 Αθήνα
e-mail: editor@psych.gr

Το δακτυλογραφημένο κείμενο πρέπει να συνοδεύεται από CD με το κείμενο της εργασίας ή να αποστέλλεται ηλεκτρονικό αντίγραφο με e-mail. Το κείμενο πρέπει να έχει γραφεί με επεξεργαστή συμβατό με πρόγραμμα Windows ή με οποιοδήποτε πρόγραμμα για υπολογιστή Macintosh.

Μαζί με τα υποβαλλόμενα άρθρα πρέπει να υποβάλλεται συμπληρωμένο το «Συνοδευτικό έντυπο υποβολής εργασίας», υπόδειγμα του οποίου υπάρχει στο τέλος κάθε τεύχους του περιοδικού. Οι υποβαλλόμενες εργασίες χαρακτηρίζονται με κωδικό αριθμό, που γνωστοποιείται στους συγγραφείς και ο οποίος χρησιμοποιείται σε κάθε επικοινωνία με το περιοδικό. Τα άρθρα γράφονται στη δημοτική γλώσσα. Η δακτυλογράφηση γίνεται στη μία όψη του φύλλου, με διπλό διάστημα και περιθώριο τουλάχιστον 3,5 cm.

Στην άνω δεξιά πλευρά της πρώτης σελίδας πρέπει να υπάρχει ο χαρακτηρισμός κάθε άρθρου (π.χ. Ανασκόπηση, Ερευνητική εργασία κ.λπ.).

ΔΙΑΤΑΞΗ ΤΗΣ ΥΛΗΣ

Όλες οι σελίδες αριθμούνται, αρχίζοντας από τη σελίδα τίτλου.

Σελίδα τίτλου: Περιλαμβάνει τον τίτλο του άρθρου (μέχρι 12 λέξεις), τα ονόματα των συγγραφέων στην ονομαστική, το κέντρο προέλευσης, τη διεύθυνση και το τηλέφωνο του συγγραφέα που θα επικοινωνεί με το περιοδικό. Στην ίδια σελίδα αναφέρονται επίσης άτομα, οργανισμοί, ιδρύματα κ.λπ., που ενδεχομένως συνέβαλαν στην πραγματοποίηση της εργασίας.

Περίληψη: Στη δεύτερη σελίδα γράφεται η ελληνική περίληψη, (περίπου 400–500 λέξεις). Στην περίληψη ανακεφαλαιώνονται τα κύρια μέρη της εργασίας. Φράσεις όπως «τα ευρήματα συζητούνται» πρέπει να αποφεύγονται. Στο τέλος της περίληψης αναγράφονται 4–6 λέξεις ευρετηρίου.

Αγγλική περίληψη: Στην τρίτη σελίδα γράφεται η αγγλική περίληψη, που πρέπει να έχει έκταση 400–500 λέξεων, ο τίτλος του άρθρου τα ονόματα των συγγραφέων και η προέλευση του άρθρου (ίδρυμα). Στο τέλος της περίληψης αναγράφονται 4–6 λέξεις ευρετηρίου. Η περίληψη πρέπει να δίνει ουσιαστικές πληροφορίες.

Κείμενο: Χωρίζεται σε κεφάλαια. Για τις ερευνητικές εργασίες είναι: Εισαγωγή, Υλικό και μέθοδος, Αποτελέσματα, Συζήτηση. Όσα αποτελέσματα παρατίθενται στους πίνακες δεν επαναλαμβάνονται λεπτομερώς στο κείμενο.

Βιβλιογραφικές παραπομπές: Αριθμούνται με αύξοντα αριθμό, ανάλογα με τη σειρά εμφάνισής τους στο κείμενο (σύστημα Vancouver). Π.χ. *Ο Birley*[1] *βρήκε ότι..., αλλά ο Afford*[2] *διαφώνησε...* Αναφέρονται τα ονόματα όλων των συγγραφέων. Στον βιβλιογραφικό πίνακα περιλαμβάνονται μόνον οι βιβλιογραφικές παραπομπές που υπάρχουν στο κείμενο. Στα άρθρα ανασκόπησης και τα ειδικά άρθρα οι βιβλιογραφικές παραπομπές δεν πρέπει να υπερβαίνουν τις 100, στις ερευνητικές εργασίες και τα γενικά άρθρα τις 50, στα σύντομα άρθρα και τις ενδιαφέρουσες περιπτώσεις τις 15 και στα άρθρα σύνταξης και τις επιστολές προς τη σύνταξη τις 8. Ο βιβλιογραφικός κατάλογος συντάσσεται με αύξοντα αριθμό, που αντιστοιχεί στη σειρά εμφάνισης των βιβλιογραφικών παραπομπών στο κείμενο, όπως στα ακόλουθα παραδείγματα:

1. Birley JLT, Adear P, Singer D, Rosenberg M. Electrogastrographic studies in elderly patients. *Gastroenterology* 1980, 79:311–314 (Περιοδικό)

2. Alford J, Nemiah J. Peptic ulcer in childhood. In: Sodeman WA (ed) *Pathologic Physiology*. Saunders, Philadelphia, 1970:457–472 (Κεφάλαιο βιβλίου)

3. Kinden A. *Stress and emotion*. Springer, Berlin, 1990 (Βιβλίο)

4. Larsen E, Elliot B. Fatigue in major depression. *Psychiatriki* 2007, (Suppl 1):S143–S144 (Παράρτημα περιοδικού)

5. Silverstone A, Leman H, Stark J. *Attempted suicide by drug-overdose*. Paper presented at 2nd Congress on Suicide behaviour, 4–6 May 2002. Rome, Abstracts Book, pp 212–213 (Παρουσίαση σε Συνέδριο - Τόμος Πρακτικών)

6. Henry A, Andrews B. *Critical issues for parents with mental illness*. N.Y. Centre for Mental Health Services 2001 (Cited 2 June 2005) Available from www. mentalorg/publications (Ιστοσελίδα)

Οι συντμήσεις των περιοδικών πρέπει να γίνονται με βάση το *Index Medicus*.

Πίνακες: Γράφονται με διπλό διάστημα γραφομηχανής σε ξεχωριστή σελίδα. Αριθμούνται ανάλογα με τη σειρά εμφάνισής τους στο κείμενο, με αραβικούς αριθμούς (πίνακας 1), ακολουθεί σύντομη κατατοπιστική λεζάντα (π.χ. Ασθενείς που νοσηλεύθηκαν για ψευδοκύηση στο Νοσοκομείο «Αλεξάνδρα» κατά το 1988) και σε κάθε στήλη υπάρχει κατατοπιστική επικεφαλίδα. Αποφεύγονται οι κάθετες γραμμές.

Εικόνες: Πρέπει να στέλνονται είτε τα πρωτότυπα των σχεδίων (με σινική μελάνη) είτε φωτογραφίες. Στο πίσω μέρος πρέπει να αναγράφεται με μολύβι ο αριθμός της εικόνας, οι συγγραφείς και ο τίτλος της εικόνας. Όλες οι εικόνες πρέπει να αναφέρονται στο κείμενο και να αριθμούνται με αραβικούς αριθμούς.

Ονοματολογία και μονάδες μέτρησης: Για λεπτομέρειες, βλ. Ιατρική 1980, 37:139.

Διόρθωση τυπογραφικών δοκιμίων: Οι συγγραφείς είναι υποχρεωμένοι να κάνουν μία διόρθωση των τυπογραφικών δοκιμίων. Εκτεταμένες μεταβολές δεν επιτρέπονται.

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Authors' signature Date

ΣΥΝΟΔΕΥΤΙΚΟ ΕΝΤΥΠΟ ΥΠΟΒΟΛΗΣ ΕΡΓΑΣΙΑΣ ΣΤΟ ΠΕΡΙΟΔΙΚΟ *"ΨΥΧΙΑΤΡΙΚΗ"*

(Υποβάλλεται μαζί με την εργασία, τρία φωτοαντίγραφα της εργασίας και την αντίστοιχη δισκέτα ή με την αποστολή ηλεκτρονικού αντιγράφου με e-mail)

- Παρακαλώ συμπληρώστε/τσεκάρετε όλα τα σημεία του εντύπου
- Είδος εργασίας (σημειώστε με Χ):

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❑ ΕΙΔΙΚΟ ΑΡΘΡΟ ❑ ΓΕΝΙΚΟ ΑΡΘΡΟ ❑ ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΠΤΩΣΕΩΣ

- Τίτλος εργασίας .....

.....

- Ονοματεπώνυμα συγγραφέων .....

.....

.....

.....

- Φορέας ή Κέντρο (α), από το οποίο προέρχεται η εργασία .....

.....

.....

- Υπεύθυνος συγγραφέας για την αλληλογραφία .....

Ονοματεπώνυμο .....

Διεύθυνση .....

Τηλέφωνο ..... Fax: ..... E-mail: .....

- Επιβεβαιώστε (σημειώστε με Χ) όλα τα παρακάτω σημεία της εργασίας μας:
  - ❑ Περίληψη της εργασίας στα ελληνικά και αγγλικά, σύμφωνα με τις προδιαγραφές του περιοδικού
  - ❑ 4–5 λέξεις ευρετηρίου στα ελληνικά και στα αγγλικά
  - ❑ Αντιστοιχία των βιβλιογραφικών αναφορών του κειμένου με τον κατάλογο της βιβλιογραφίας, που παρατίθεται στο τέλος του άρθρου
  - ❑ Καταγραφή των βιβλιογραφικών αναφορών σύμφωνα με τις προδιαγραφές της «*Ψυχιατρικής*»

Οι συγγραφείς της εργασίας συμφωνούν με το περιεχόμενο της, τη δημοσίευσή της στο περιοδικό "Ψυχιατρική" και τη μεταβίβαση των συγγραφικών δικαιωμάτων στο περιοδικό. Το ίδιο κείμενο δεν έχει δημοσιευθεί ούτε έχει υποβληθεί για δημοσίευση σε άλλο περιοδικό. Οι συγγραφείς δεν έχουν αντικρουόμενα συμφέροντα σε σχέση με το περιεχόμενο της εργασίας και δηλώνουν ότι το πρωτόκολλο της έρευνας εγκρίθηκε από την Επιτροπή Βιοηθικής του Ιδρύματος όπου πραγματοποιήθηκε η έρευνα. Όλα τα άτομα που συμμετείχαν έδωσαν τη συγκατάθεσή τους πριν συμπεριληφθούν στην έρευνα. Οι συγγραφείς ακόμη δηλώνουν ότι δεν υπήρξε πηγή οικονομικής υποστήριξης (εάν υπήρξε πρέπει να δηλωθεί).

Υπογραφές συγγραφέων Ημερομηνία