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EDITORIAL

Individualized music for dementia: Evolution and application of evidence-based protocol

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Abstract

The theory-based intervention of individualized music has been evaluated clinically and empirically leading to advancement and refinement of an evidence-based protocol, currently in its 5th edition. An expanded version of the protocol was written for professional health care providers with a consumer version tailored for family caregivers. The underlying mid-range theory is presented along with a seminal study that was followed by further research in the United States, Canada, Great Britain, France, Sweden, Norway, Japan and Taiwan. Key studies are summarized. Given its efficacy when implemented by research staff, studies have advanced to testing the intervention under real-life conditions when implemented and evaluated by trained nursing assistants in long-term care facilities and visiting family members. In addition, one study evaluated the implementation of music by family members in the home setting. Initial research focused on agitation as the dependent variable with subsequent research indicating a more holistic response such as positive affect, expressed satisfaction, and meaningful interaction with others. The article advances by describing on-line programs designed to train health care professionals in the assessment, implementation and evaluation of individualized music. In addition, Gerdner has written a story for a picture book intended for children and their families (in press). The story models principles of individualized music to elicit positive memories, reduce anxiety and agitation, and promote communication. The article concludes with implications for future research.

Key words: Individualized music; Dementia; Alzheimer's disease; Agitation; Evidence-based protocol

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SIGNIFICANCE

In 2009, Alzheimer's Disease International[1] estimated by 2010 there would be 35 million people worldwide afflicted with Alzheimer's disease and related dementias (ADRD). This organization also predicted that the prevalence of ADRD would nearly double every 20 years for a total of 65.7 million people afflicted with the disease by 2030 and 115.4 million by 2050[1].

ADRD is characterized by cognitive impairment. Researchers[2] estimate the presence of agitation in 70% to 90% of persons in the advanced stages of ADRD. Agitation interferes with care delivery and social interaction, ultimately having a negative impact on the person's quality of life[3].

THEORY-BASED INTERVENTION

Gerdner[4] was the first to develop and test a research

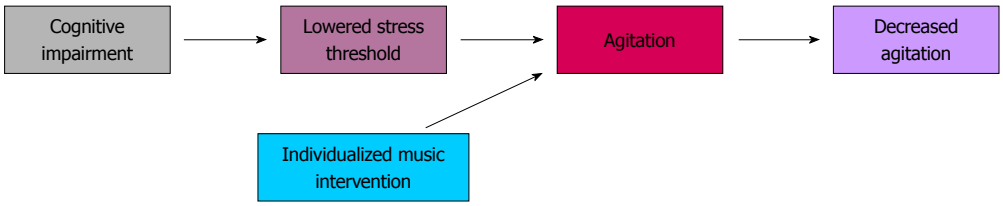

Figure 1 Gerdner's mid-range theory of individualized music intervention for agitation [11].

protocol to evaluate the use of individualized music as an alternative intervention for the management of agitation in persons with ADRD. Individualized music is defined as music that has been integrated into the person's life and is based on personal preference[4]. Publication of this pioneer pilot study[5] led to additional research, with findings that support the use of individualized music in reducing agitation in persons with ADRD[6-10].

Gerdner[11] advanced this work by developing a theoretical foundation for this intervention. Elements of the mid-range theory of individualized music intervention for agitation (IMIA) include: cognitive impairment, progressively lowered stress threshold, agitation, and individualized music (Figure 1).

Cognitive impairment, as found in persons with ADRD, is a key antecedent to agitation. Hall *et al*[12] attribute this to a decreased ability to receive and process sensory stimuli, resulting in a progressive decline in the person's stress threshold and a heightened potential for anxiety. In other words, as the disease progresses, fewer stressors are required to meet and exceed the stress threshold, resulting in anxious and agitated behaviors[12]. Cohen-Mansfield *et al*[13] define agitation as an "inappropriate verbal, vocal or motor activity that is not explained by need and confusion *per se*". They further explain that although agitation probably results from a combination of needs and confusion, these antecedent conditions are not always apparent[13].

Individualized music may be used as an alternative intervention for the management of agitation in ADRD. The intervention involves carefully selected music, based on the person's preference, prior to the onset of cognitive impairment. Gerdner[11] theorizes that music may be used as a means of communicating with the person even in the advanced stages of ADRD when the person has an impaired ability to understand verbal language and has a decreased ability to interpret environmental stimuli. It is further theorized that the presentation of individualized music will provide an opportunity to stimulate remote memory. This changes the focus of attention and provides an interpretable stimulus, overriding stimuli in the environment that is meaningless or confusing. The elicitation of memories associated with positive feelings will have a soothing effect on the person with dementia, which in turn will prevent or alleviate agitation[11]. It is further theorized that individualized music is most effective when it is implemented prior to the peak level of agitation.

SEMINAL STUDY

The strengths and limitations of preliminary research were used to design a more rigorous study with a larger sample for the purpose of testing the propositions of the mid-range theory of IMIA. Gerdner[14] employed an experimental repeated measures pretest-posttest crossover design to compare the immediate and residual effects of individualized music to classical "relaxation" music relative to baseline on the frequency of agitated behaviors in persons with ADRD. Thirty-nine subjects were recruited from six long-term care facilities in Iowa. The sample consisted of 30 women and 9 men (mean age, 82 years) with severe cognitive impairment, as measured by the Global Deterioration Scale[15]. Baseline data were collected for 3 wk. Family members completed a written questionnaire that was reviewed by the investigator. Answers were explored with the informant to refine information as a means of determining specific music selections. Subjects were divided into two groups. Group A (n = 16) received individualized music for 6 wk followed by a 2-wk "washout" period and 6 wk of classical "relaxation" music. Group B (n = 23) received the same protocol but in reverse order. The interventions consisted of pre-recorded music presented for 30 min, two times per week. A modified version of the Cohen-Mansfield Agitation Inventory[16] was used to measure the dependent variable. A repeated measures analysis of variance with Bonferroni post hoc test showed a significant reduction in agitation during and following individualized music compared to classical "relaxation" music.

This study became the impetus for additional studies conducted in the United States, Canada, Great Britain, France, Sweden, Norway, Japan and Taiwan. These efforts have resulted in an expanding body of research that supports the use of this intervention for the management of agitation[17-24]. In addition, a study is currently being conducted in Iran to further test the effects of individualized music.

EVIDENCE-BASED PROTOCOL

Gerdner's work served as the foundation for an expanding body of empirical and clinical evidence, leading to development of the evidence-based protocol of Individualized Music for Elders with Dementia. This protocol was originally published in 1996 with the 5th and most recent version published in 2007[25]. This expanded version was specifically written for professional health care providers.

The protocol identifies risk factors for agitation, assessment criteria, a detailed description of the intervention, evaluation of patient outcomes and process factors. An evidence grade schema is used to assign a specific grade, based on the strength and type of evidence, for each recommendation within the protocol. To facilitate accessibility an abridged and updated version of the protocol was published in a 2010 issue of the *Journal of Gerontological Nursing*[26].

Following instruction, family members may also implement individualized music. Consequently a companion consumer version was added to the evidence-based protocol in 2001 and updated in 2007[27]. The consumer version provides a simplified format, tailored for family caregivers.

The evidence-based protocol includes The Assessment of Personal Music Preference Questionnaire (APMPQ)[28] that has been developed and tested[17] to assist in the selection of individualized music. Questions are used to explore the meaning of music in the person's life and identify preferred song titles. Because musical selections are often closely aligned with specific performers this also become an important part of the assessment process. When cognitive impairment prevents the person from identifying or expressing these preferences an alternate version of the questionnaire is available for completion by a close family member. The alternate version of APMPQ has been successfully used by family members of residents living in long-term care facilities[17] and those who care for an elder at home[19].

The expected effect of individualized music is dependent on the identification and implementation of music based on the patient's specific music preferences. For example, one older woman's favorite music was an LP record (now available on compact disc) performed by Elvis Presley entitled, *Amazing Grace: His Greatest Sacred Performances*.

Individualized music may not be suitable for everyone. For example, it would not be appropriate for a person who did not have an appreciation for music prior to the onset of cognitive impairment. A positive correlation is expected between the degree of significance that music had in the person's life prior to the onset of dementia and effectiveness of the intervention[25].

ADVANCING THE SCIENCE

There is need to advance the science by evaluating the effects of individualized music using biophysiological outcome measures. Japanese researchers, Suzuki *et al*[21] incorporated preferred music into a small group singing activity for persons with ADRD. Outcome measure included biophysiological measures in addition to behavioral outcome measures. The study involved 10 subjects with dementia who participated in the music sessions twice per week for 8 wk. During the corresponding time period, 13 subjects participated in a comparison intervention (i.e., games, drawing, pasting pictures). Analysis compared baseline data to 1-wk post intervention scores. Findings indicated that subjects in the experimental group had a statistically significant improvement in the "language" subscale of the Mini Mental State Exam and a statistically significant reduction in "irritability" as measured by the Multidimensional Observational Scale. In addition, there was a statistically significant reduction in stress index as measured by salivary chomogranin A (CgA) following session 16. The authors concluded, "the changes in CgA levels supported Gerdner's mid-range theory" (p. 17). No significant findings occurred in the control group across outcome measures. It is important to note that music sessions in this study deviated from the evidence-based protocol of individualized music by incorporating active participation (i.e., singing).

Suzuki *et al*[22] expanded this research by incorporating immunoglobulin A (IgA) as well as saliva CgA and behavioral outcome measures. The study tested a small group music intervention, based on the music preferences of eight persons with dementia. One person refused saliva sampling and researchers were unable to obtain saliva sampling from a second. The experimental group was compared to a control group, over a 3-mo period. Findings included a statistically significant reduction in salivary CgA with no significant change in IgA. The researchers once again concluded that this findings support Gerdner's mid-range theory.

ANXIETY IN RELATIONSHIP TO AGITATION

As described by Hall *et al*[12], anxiety is closely related to agitation. Without intervention, anxiety may escalate to agitation. The subtle cues of cumulative stress are often overlooked, advancing to agitated behaviors that present with increased frequency and intensity[12,29]. As previously explained, individualized music should be implemented prior to the peak level of agitation, ideally when the person first begins exhibiting subtle behavioral signs and symptoms[11].

Sung *et al*[30] conducted a study in Taiwan to evaluate the evidence-based protocol of individualized music on the outcome measure of anxiety. Trained nursing staff implemented the protocol for 23 persons with ADRD, who resided in a long-term care facility. The researchers adapted *The Assessment of Personal Music Preference Questionnaire*[28] to be culturally meaningful for the Taiwanese and Chinese sample. The outcome variable was measured using the Rating Anxiety in Dementia[31] tool. It should be noted that some items such as restlessness overlap with items represented on the Cohen-Mansfield Agitation Inventory[16]. The intervention was implemented biweekly for 6 wk. Statistical analysis was conducted using an ANCOVA. Persons in the experimental group had a significantly lower level of anxious behaviors ($F = 12.15$, $P = 0.001$) when compared to the control group who received "standard care".

Similarly, a study conducted by Guetin *et al*[32] in France evaluated the effects of preferred music on persons in the early to moderate stages of Alzheimer's disease. Anxiety, as measured by the Hamilton scale, was incorporated as an outcome variable. A significant reduction in anxiety was identified during the implementation of individualized music.

TRANSLATING RESEARCH INTO PRACTICE

Given its efficacy when implemented by research staff, it is important to evaluate the effectiveness of individualized music when implemented under real-life conditions. As a beginning effort, Gerdner[17] conducted a pilot study using mixed methods to evaluate the effects of individualized music when implemented by staff and family. Following training, staff and family implemented individualized music for eight persons with moderate to severe stages of dementia, living in a long-term care facility. The intervention was implemented over a 4-wk period. Individualized music was played daily for 30 min at a prescribed time (prior to the estimated "peak level" of agitation). The mean rate of compliance was 86.3%. In addition, staff administered music on an "as needed" basis (when the person first began exhibiting signs of agitation). Agitation was measured using a modified version of the Cohen-Mansfield Agitation Inventory[16]. A statistically significant reduction in agitation was found during the presentation of music, with an overall reduction in agitation on day shift during weeks 1-8 and on evening shift during weeks 5-8. Staff and family interviews provided convergent validity to quantitative findings. In addition, staff and family reported that individualized music provided a catalyst for meaningful interaction between the person with dementia and others.

Researchers in Taiwan also evaluated the use of individualized music when implemented by trained staff in a long-term care facility. Findings were published as two separate articles.

In one article, Sung *et al*[24], focused on knowledge of and adherence to the evidence-based protocol for individualized music when implemented by 17 nursing staff, working in a long-term care facility in Taiwan. Initial training included an interactive educational program. Ongoing reminders, a local opinion leader, and an audit checklist were used to facilitate and monitor continued adherence to the intervention protocol. Analysis used to compare pre and post-test scores found a statistically significant improvement ($P < 0.001$) in knowledge of the intervention following the training session with a mean compliance of 72%.

In a companion study, Sung *et al*[23], focused on the resident's response to individualized music when implemented by trained nursing staff. The Cohen-Mansfield Agitation Inventory[16] was used to measure the dependent variable. The sample included an experimental group ($n = 32$) that received individualized music for 30 min, twice per week over 6 wk. The control group ($n = 25$) received usual care without music. Findings showed that the experimental group had a statistically significant reduction in overall agitation ($t = -2.19$, $P < 0.05$) and physically non-aggressive behaviors ($t = -3.75$, $P < 0.0001$) compared to the control group.

In another published study, Park *et al*[33] report 20 in-home family caregivers were trained in the use of the evidence-based protocol for individualized music. Outcome measures included the modified Cohen-Mansfield Agitation Inventory[16]. A quasi-experimental design was used in which individualized music was implemented two times per week for 2 wk. Statistical analysis identified a significant reduction in agitation during the intervention period compared to baseline and post-intervention periods.

Park's dissertation, the study of origin[19], added a quantitative measure for pain in addition to agitation. It is important to note that the evidence-based protocol for individualize music identifies pain as a risk factor for agitation. The protocol also cautions that agitation, secondary to a medical condition, requires treatment of the underlying cause. Under these conditions, individualized music may be used to supplement medical care.

Gallagher[34] studied the feasibility of training palliative care staff in the use of individualized music for management of agitation, during the advanced stage of dementia. Twenty-four hospice professionals were trained in the evidence-based protocol. Feasibility was assessed through the participants' knowledge and confidence in using the protocol. Findings support the practicality of training multidisciplinary staff in the implementation of individualized music.

In addition, Oslo Resource Center for Dementia and Psychiatric Care of the Elderly, under the direction of Dr. Audun Myskja, implemented the evidence-based protocol of individualized music in three nursing homes in Oslo, Sweden and has incorporated the intervention into a complementary therapy module designed with academic credits for a master's degree at Buskerud University College[35].

ON-LINE TRAINING

Continuing efforts are underway to promote and support the use of individualized music by clinicians. For example, Gerdner collaborated with Sigma Theta Tau International and the John A. Hartford Foundation for the development of a free interactive on-line continuing educational module to assist nurses in the assessment, implementation, and evaluation of individualized music. The module was first incorporated into the evidence-based protocol in 2004 and was updated in 2008[36].

The module includes a case example, based on a real-life incident with names changed to protect confidentiality. The case example highlights the need to consider cultural background when assessing musical preference.

It involves an Italian American woman who spoke minimal English. Her preferred music includes recordings of Dean Martin singing Italian songs.

Nurse participants of the module are asked to complete an evaluation of the course. The overwhelming majority rated the content as excellent and reported that it would help them in their practice.

The New York State Department of Health has developed a series of free multi-disciplinary on-line training modules referred to as the *Electronic Dementia Guide for Excellence* (EDGE). One of the modules specifically focuses on individualized music[37]. The module provides specific guidelines for the development of a 45-min in-service, including learning objectives and a PowerPoint presentation. A sample case study is provided to assist the learner in the application of this knowledge for the assessment, implementation, and evaluation of individualized music. The module is reported to be one of the most popular in the EDGE series.

FACILITATORS FOR INTERVENTION

Individualized music was developed as an alternative intervention for the management of agitation in persons with ADRD. The intervention promotes a humanistic, individualized approach to care. The use of pre-recorded music does not require special musical abilities and can therefore be implemented by trained staff and family caregivers. The recipient's positive response to individualized music has been identified as a facilitator for its continued use by staff and family[17]. The process of assessing and implementing music has been shown to promote a collaborative working relationship between staff and family[17]. Anecdotal notes and qualitative interviews also indicate that individualized music promotes positive affect, expressed satisfaction, and meaningful interaction with others; thereby supporting personhood[17].

PICTURE BOOK FOR CHILDREN AND THEIR FAMILIES

In 2011, the Alzheimer's Association[38] estimated that over 5.4 million Americans had a diagnosis of ADRD with nearly 15 million nonpaid persons caring for someone with the disease. Twenty-six percent of family caregivers have children, younger than 18 years of age, living with them[38]. Social worker, Elizabeth Smith-Bovin, declares "children as the forgotten victims of Alzheimer's disease"[39].

Research indicates that the signs and symptoms associated with dementia adversely affect communication and relationships between afflicted grandparents and their grandchildren[40,41]. A child's response to a person with Alzheimer's disease will vary depending on factors such as: the child's age, the number of other children in the family, the closeness of the relationship between the child and the afflicted person, the availability of other family members, and the cultural background of the child[42].

Overall, children should be encouraged to ask questions, express feelings openly[43] and remain involved with the person at a level that is appropriate to the child's ability and understanding[42]. Illustrated children's books with stories that describe children's reactions to Alzheimer's disease can be used to model ways for them to interact with people who have the disease[44,45].

While there are a number of children's books on the market that address Alzheimer's disease, the majority provide an oversimplification of the disease and introduce the same basic content with only slight variations. These books are generally targeted for a younger audience. There is a critical need for a book of high quality for older children and their parents.

Basic principles of the evidence-based protocol of individualized have been translated into a picture book for children and their family. The book, currently in press, is authored by Gerdner and is targeted for children aged 8 to 12 years of age[46]. However, the underlying message of understanding and compassion transcends to persons of all ages. The story entitled, *Musical Memories*, is about Gabrielle and her grandmother who has Alzheimer's disease. It provides an honest and respectful depiction of an older person with this disease. The story is unique in that it reflects our current knowledge and understanding of the disease. The story goes beyond the issue of short-term memory to address antecedents of anxiety progressing to agitation. *Musical Memories* promotes a problem solving approach that models the use of a simple intergenerational activity (listening to music) to empower the child in maintaining a relationship with her grandmother. Author notes, located at the end of the book, directly relate to and build upon the story content to strengthen the educational value of the book.

RESEARCH IMPLICATIONS

The accumulation of clinical and empirical data provides a strengthening body of evidence that supports the use of individualized music for persons with ADRD. As research evolves, methods and outcome measures are beginning to capture a more global response to the intervention. There is need to test the evidence-based protocol of individualized music using a stress index measure such as, salivary CgA. In addition, anecdotal data and findings from open-ended interviews indicates a positive behavioral response while listening to preferred music that "illuminates personhood" of the listener[5,14,17]. However, the recipient's positive response needs to be measured through more quantifiable outcome measures. There is also need to design large feasibility studies that evaluate the cost effectiveness of individualized music when implemented by staff in long-term care facilities.

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ORIGINAL ARTICLE

Risks of suicidality in adult patients with epilepsy

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Abstract

AIM: To determine the prevalence and risks of suicidality in a group of patients with epilepsy.

METHODS: Included were 200 adult patients and 100 matched healthy subjects. The clinical interview using The Diagnostic and Statistical Manual of Mental Disorders (4th edition), Beck Depression Inventory (2nd edition) (BDI-Ⅱ), Hamilton Anxiety Rating Scale (HAM-A), Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Eysenck Personality Questionnaire-Revised Rating Scale testings were used for diagnosis and assessment of severity of psychiatric symptoms. Blood concentrations of serotonin, catecholamines and dopamine were also measured.

RESULTS: Suicidality was reported in 35% (compared to 9% for controls), of them 80%, 72.86%, 55.71% and 52.9% had depression, anxiety, obsession and aggression respectively. Patients with suicidality had higher scores of BDI-Ⅱ (P = 0.0001), HAM-A (P = 0.0001), and Y-BOCS (P = 0.037) and lower scores of psychotic (P = 0.0001) and extroversion (P = 0.025) personality traits. Regardless the presence or absence of suicidality, patients with epilepsy had low serotonin (P = 0.006), noradrenaline (P = 0.019) and adrenaline (P = 0.0001) levels. With suicidality, significant correlations were identified between: (1) age and scores of BDI-Ⅱ (r = 0.235, P = 0.0001) and HAM-A (r = 0.241, P = 0.046); (2) age at onset and concentrations of noradrenaline (r = -0.502, P = 0.024); (3) duration of illness and scores of BDI-Ⅱ (r = 0.247, P = 0.041), Y-BOCS (r = 0.270, P = 0.025) and neurotic personality trait (r = -0.284, P = 0.018); and (4) doses of antiepileptic drugs and scores of psychotic personality traits (r = -0.495, P = 0.006 for carbamazepine; r = -0.508, P = 0.0001 for valproate).

CONCLUSION: This is the first study which systematically estimated the prevalence and risks of suicidality in a homogenous group of patients with epilepsy. This study emphasizes the importance of epilepsy itself as a risk for suicidality and not its treatment.

Key words: Epilepsy; Anti-epileptic drugs; Psychosocial variables; Serotonin; Catecholamines; Dopamine

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INTRODUCTION

Epilepsy is one of the most important and common chronic medical problems with prevalence rate of 8.2-12.9 per 1000 in general population[1]. Fortunately 70% of patients with epilepsy become seizure free on antiepileptic drugs (AEDs) while the remaining had medically refractory seizures (interactable epilepsy). In such patients, resection of the region of of the brain causing seizures is one approach of treatment[2]. The research literature indicates that people with epilepsy are at higher risk for suicide and suicidality (suicidal thoughts and attempts) with an estimated lifetime prevalence rate that varies between 3.3% and 14.3% or even up to 32.5%. This rate has been reported to be 6 to 25 times higher with temporal lobe epilepsy (TLE)[3,4] compared to 1.4%-6.9% in general population[5] and even higher for those who had temporal lobectomy[2]. Suicide accounts for > 10% of deaths with epilepsy compared with 1.4% in general population[6].

Suicidality in patients with epilepsy has complex and multifactorial aetiologies. Several factors have been identified as risks which include: male sex[6], early age at onset[7,8], TLE, high frequency of primary generalized seizures, polymorphic seizures combination, severe epilepsy, lateralization of the epileptic focus, recent control of seizures, absence of seizures for a long time especially after being very frequent, cognitive deterioration and hypofrontality and psychiatric comorbidity[6-9]. Retrospective studies indicate that the majority (81%-100%) of suicides occurs in subjects with psychiatric illnesses of which depression is the most common with a risk of 15%-18.9%, and even as high as 50 times than of general population. Others include anxiety, mood disorders and epileptoid personality and past or family histories of psychiatric disorders[6-9].

Recently, AEDs have been suggested as a risk of suicide with epilepsy[10,11]. The mechanisms of the negative psychotropic effects of AEDs are complex and vary dramatically between patients. It has been suggested to be related to the direct (i.e., anticonvulsant action) and indirect mechanisms of the drug action, particulary with rapid dose titration, slow drug metabolism, polypharmacy, drug-drug interactions, drug toxicity, drug withdrawal and metabolic derangements (as folate deficiency)[12]. Also non-pharmacological treatments as surgery[2] and vagus nerve stimulation[13] have been suggested to increase the risk of suicide up to 5-folds higher than pharmacological therapy. The concept of forced normalization (or alternative psychosis) in which a good control of seizures regardless control of EEG changes by pharmacological and non-pharmacological therapy results in appearance of behavioral abnormalities or psychosis, has been suggested as a cause of behavioral adverse effects or even suicid, although the exact mechanisms are not fully understood[14].

Despite the above information, the prevalnece of suicidality and the spectrum of comorbid psychiatric disorders with epilepsy tended to range greatly from one study to another. This reflects the heterogeneity of epilepsy and the differences in study designs and studied populations.

Early recognition and possible modification of clinical and psychosocial variables will have significant impact on the medical management and quality of life of patients with epilepsy.

To our knowledge, this is the first study in our population which aimed to estimate the prevelance and risks of suicidality in a homogenous group of patients with epilepsy.

MATERIALS AND METHODS

The out-patient epilepsy clinic of Assiut University Hospital manages patients with epilepsy who were not covered by insurance service and all families were of low-income. The number patients of epilepsy of unknown etiology (idiopathic epilepsy) attending the clinic monthly for follow up is 601 (adults = 474 and children = 127). Clinical psychiatric interviewing was the primary method for examining the patients and in addition by applying the criteria for diagnosis of Diagnostic and Statistical Manual of Mental Health Disorders (4th edition) (DSM-IV)[15]. Accordingly, patients were divided into two groups: (1) those with no psychiatric symptoms (n = 107); and (2) those without psychiatric symptoms (n = 367). Also 100 healthy subjects matched for age, sex, educational level and socioeconomic states were included as controls for statistical comparisons. Healthy subjects were recruited from the general population. The patient's seizure type was diagnosed according to Berg *et al*[16] Revised terminology and concepts for organization of seizures and epilepsies: report of The International League Against Epilepsy Commission on Classification and Terminology, 2005-2009". Excluded were subjects with: (1) intelligence quotient < 70 as assessed by the Arabic version of Wechsler Adult Intelligence Scale Revised[17,18]; (2) other neurologic, systemic or medical diseases that result in psychiatric abnormalities; (3) psychiatric disorder prior to the onset of epilepsy; (4) regular medication(s) in addition to AEDs; and (5) alcoholism or substance abuse. The study protocol was approved by the ethical committee of The Faculty of Medicine of Assiut University and all participants gave their informed consent to participate in the study.

Neurological evaluation included information regarding seizure variables (as age at onset, precipitating factors, duration of illness, type and frequency of seizures, type of utilized AED(s), duration of treatment, degree of control on AEDs and family history of psychiatric illness. The frequencies of seizures were defined as described before[19] as follow: (1) very frequent: occurring several

times a day or at intervals shorter than 7 d; (2) frequent: occurring at intervals longer than 7 d but shorter than 30 d; (3) occasional: occurring at intervals longer than 30 d but shorter than 1 year; and (4) rare: occurring at intervals longer than 1 year. Regarding the degree of control on AEDs, patients were considered controlled when seizure free for ⩾ 1 year, partially controlled when seizure were occasional or rare and uncontrolled when seizures were frequent or very frequent.

Patients were divided into two groups according to the presence or absence of sucidality. The following Arabic translated questionnaires and scales were used for screening and assessment of severity of psychiatric symtoms and disorders: (1) Beck Depression Inventory (2nd edition) (BDI-Ⅱ)[20,21]; (2) Hamilton Anxiety Rating Scale (HAM-A)[22,23]; (3) Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[24,25]; and (4) Eysenck Personality Questionnaire-Revised Rating Scale (EPQ-R)[26,27].

BDI-Ⅱ consists of 21 items and each corresponds to a symptom of depression is summed to give a single score. Accordingly, subjects were divided into: (1) those with no or minimal symptoms (scoreing: 0-13); (2) those with mild symptoms (scoring: 14-19); (3) those with moderate symptoms (scoring: 20-28); and (4) those with severe symptoms (scoring: 29-63). HAM-A consists of 14 items, each is scored on a 5-point scale, ranging from 0 (not present) to 4 (severe). Accordingly, subjects were divided into: (1) those with no anxiety symptoms (scoring: 0-13); (2) those with mild symptoms (scoring: 14-17); (3) those with moderate symptoms (scoring: 18-20); and (4) those with severe symptoms (scoring: 25-30). Y-BOCS is formed of two subscales: obsessions and compulsions. Each subscale consists of 5-items: (1) time spent in the symptoms; (2) subjective distress; (3) interference from symptoms; (4) resistance from symptoms; and (5) control over symptoms. Each item is scored from 0 (no symptoms) to 4 (extreme symptoms). The total Y-BOCS score ranges from a minimum of 0 to a maximum of 40. Accordingly, subjects are divided into: (1) those with no OCSs (scoring: 0-7); (2) those with mild symptoms (scoring: 8-15); (3) those with moderate symptoms (scoring: 16-23); (4) those with severe symptoms (scoring: 24-31); and (5) those with extreme symptoms (scoring: 32-40). EPQ-R consists of 4 scales: (1) Extroversion (E) which is formed of 23 items; (2) Neuroticism (N) which is formed of 24 items; (3) Psychoticism (P) which is formed of 32 items; and (4) social desirability or Lie (L) which is formed 21 items. Each scale is measured and has a dichotomous response format (yes or no).

Laboratory investigations: Subjects included in this study were controlled for timing of blood samples which were drawn at (8.00-10.00 am) after an overnight fast and patients were seizure free for at least 72 h (as any postictal central neurochemical dysfunction, is recognized to reverse within hours). The following laboratory tests were done: (1) Standardized which included: measurements of complete blood count and levels of creatinine, liver enzymes and fasting blood glucose; and (2) Specific which included: measurements of serum levels of serotonin and plasma levels of catecholamines (adrenaline and noradrenaline) and dopamine. The levels of serotonin, catecholamines and dopamine were measured by enzyme immunoassay method kits (IBL international GMBH, Hamburg, Germany). For confirmation, levels were assessed twice at two different days and combined with the cross sectional assessment while clinical evaluation and interviewing of included subjects. The serum levels of AEDs were measured as part of the investigation in batched assays in The Therapeutic Drug Monitoring laboratory of Assiut University hospital, Assiut, Egypt using Fluorescence Polarization Immunoassay System of Abbott, TDxFLX apparatus (Abbott Lab, Wiesbaden, Germany). The approximated reference therapeutic serum level of carbamazepine (CBZ) was 4-10 μg/mL and 50-100 μg/mL for valproate (VPA)[19].

Statistical analysis

Calculations were done with the statistical package SPSS, version 12.0. Kolmogorov-Simirnov test was used to test the parameter distributed. Data were presented as mean ± SD when normally distributed and mean (quartiles) if did not normally distributed (e.g., scores of BDI-Ⅱ and HAM-A and blood levels of serotonin, catecholamines and dopamine). Student's *t* test was used for comparison of means of normally distributed parameters while Mann-Whitney *U* test was used for comparison of non-normally distributed parameters. Correlations were assessed using Pearson's test for normally distributed data and Spearman's coefficient for non-normally distributed data. For all tests, values of $P < 0.05$ were considered statistically significant.

RESULTS

This study included 200 adults (males = 100; females = 100) with epilepsy psychiatric symptoms. Their ages ranged between 20 to 48 years (mean: 30.47 ± 7.56 *vs* 29.14 ± 6.90 for control subjects; $P = 0.229$) and duration of illness ranged from 3 to 35 years (mean: 13.94 ± 7.24). The majority (62%) had complex partial or partial epilepsy with secondary generalization, while 38% had generalized tonic-clonic convulsions (GTC). Sixty patients (32.2%), 58 (46.77%) and 5 (4.03%) had frontal, temporal (TLE) and parietal lobe epilepsies. Seventy four (59.68%) had left sided foci of epileptic activity while 50 (40.32%) had right sided foci. The majority of patients were treated with CBZ (57%, $n = 114$ and/or VPA 19%, $n = 38$ and 24%, $n = 48$, respectively) for 2-30 years (mean: 9.28 ± 4.02). The majority of patients (54.0%, $n = 108$) were uncontrolled on AEDs, 23.5% ($n = 47$) were partially controlled and 22.5% ($n = 45$) were controlled.

Suicidatlity was reported in 35% (suicidal attempts = 23, 32.9%, suicidal thoughts = 47, 67.1%; male = 34, 17%; female = 36, 18%) compared to 9% of healthy subjects (suicidal thoughts = 9, 100%; male = 4, 4%; female = 5, 5%, Table 1). The majority of patients with

Table 1 Demographic and clinical features of the studied group of epilepsy (mean ± SD) *n* (%)

Demographic and clinical features	Patients (*n* = 200)	Patients with history of suicidality (*n* = 70)	Patients without history of suicidality (*n* = 130)
Male/female	100/100	34/36	66/64
Age (yr)	20-48 (30.47 ± 7.56)	20-48 (29.33 ± 7.60)	20-48 (31.08 ± 7.50)
Age at onset of disease (yr)	1-40 (16.24 ± 8.40)	1-39 (15.46 ± 8.66)	1-40 (16.66 ± 8.26)
Duration of illness (yr)	3-35 (13.94 ± 7.24)	3-31 (13.77 ± 6.93)	3-35 (14.04 ± 7.42)
Type of epilepsy			
GTC	76 (38.0)	23 (32.9)	53 (40.8)
Complex partial/partial epilepsy with secondary generalization	124 (62.0)	47 (67.1)	77 (59.2)
Frontal	60 (48.39)	22 (46.81)	38 (49.35)
Temporal	58 (46.77)	23 (48.94)	35 (45.45)
Parietal	5 (4.03)	1 (2.13)	4 (5.19)
Occipital	1 (0.80)	1 (2.13)	0
Side of epileptic activity			
Right	50 (40.32)	22 (46.81)	28 (36.36)
Left	74 (59.68)	25 (53.19)	49 (63.63)
AED(s) utilized			
CBZ	114 (57.0)	31 (44.3)	83 (63.8)
VPA	48 (24.0)	21 (30.0)	27 (20.8)
Polytherapy	38 (19.0)	18 (25.7)	20 (15.4)
Dose of AED(s) (mg/d)			
CBZ	400-1200 (750.54 ± 350.5)	400-1200 (700.24 ± 320.25)	400-1200 (760.25 ± 300.25)
VPA	200-1400 (850.50 ± 345.7)	200-1400 (840.30 ± 305.75)	200-1400 (730.50 ± 255.7)
Duration of treatment (yr)	2-30 (9.28 ± 4.02)	2-30 (9.28 ± 4.02)	2-30 (9.38 ± 4.39)
Serum drug level (μg/mL)			
CBZ	4.30-12.80 (9.56 ± 4.5)	4.30-12.80 (9.56 ± 4.5)	4.30-12.80 (9.56 ± 4.5)
VPA	35.54-120.45 (80.50 ± 30.0)	35.54-120.4 (100.50 ± 30.0)	35.54-120.4 (85.50 ± 25.0)
Degree of control on AED(s)			
Controlled	45 (22.5)	9 (12.9)	24 (26.2)
Partially controlled	47 (23.5)	14 (20.0)	3 (25.4)
Uncontrolled	108 (54.0)	47 (67.1)	63 (48.5)

GTC: Generalized tonic-clonic; AEDs: Antiepileptic drugs; CBZ: Carbamazepine; VPA: Valproate; Controlled: Seizure free for ⩾ 1 year; Partially controlled: Occasional or rare in frequency; Uncontrolled: Very frequent or frequent in frequency.

suicidality (regardless of gender) had depression (80%). While anxiety, obsession, extroversion personality traits and aggression were reported in 72.86%, 55.71%, 21.5% and 52.9%, respectively (Tables 2 and 3). In general and regardless to the presence or absence of suicidality, patients with epilepsy had: (1) high scores of BDI-Ⅱ, HAM-A and psychotic and neurotic personality traits regardless the type and focus and side of epilepsy and type of AEDs; (2) high scores of Y-BOCS particularly with frontal lobe epilepsy ($P = 0.001$) and left foci of epileptic activity ($P = 0.015$) and regardless to the type of AEDs; (3) the lack of control of seizures on AEDs was a risk for high scores of BDI-Ⅱ ($P = 0.0001$), HAM-A (partially controlled: $P = 0.02$; uncontrolled: $P = 0.0001$) and Y-BOCS (partially controlled: $P = 0.01$; uncontrolled: $P = 0.0001$) (Table 4); (4) low serotonin concentrations particularly with GTC ($P = 0.002$) and TLE ($P = 0.003$) and with VPA ($P = 0.009$) and polytherapy ($P = 0.007$); (5) low catecholamines (noradrenaline and adrenaline) concentrations regardless the type, focus and side of epilepsy and type of AEDs; and (6) low dopamine concentrations particularly with GTC ($P = 0.051$) and lack of seizures control on AEDs ($P = 0.004$) (Table 5).

When patients with and without suicidality were compared, the former group had higher scores of BDI-

Table 2 The frequencies of psychiatric symptoms in the studied group of epilepsy *n* (%)

Psychiatric disorders	Patients (*n* = 200)	Patients with history of suicidality (*n* = 70)	Patients without history of suicidality (*n* = 130)
BDI-Ⅱ	108 (54)	56 (80.00)	52 (40)
Mild	17 (15.74)	5 (8.93)	12 (23.08)
Moderate	37 (34.26)	18 (32.14)	19 (36.54)
Severe	54 (50)	33 (58.93)	21 (40.38)
HAM-A	96 (48.0)	51 (72.86)	45 (34.62)
Mild	19 (19.79)	7 (13.73)	12 (26.67)
Moderate	30 (31.25)	14 (27.45)	16 (35.56)
Severe	47 (48.96)	30 (58.82)	17 (37.78)
Y-BOCS	102 (52.5)	39 (55.71)	66 (50.77)
Mild	45 (44.12)	13 (33.3)	32 (48.48)
Moderate	27 (26.47)	7 (17.95)	20 (30.30)
Severe	18 (17.65)	11 (28.21)	7 (10.61)
Extreme	15 (14.71)	8 (20.51)	7 (10.61)
EPQ-R			
Psychosis	71 (35.5)	13 (18.4)	58 (44.6)
Neurosis	36 (18.0)	11 (15.7)	25 (19.2)
Extroversion	33 (16.5)	5 (7.1)	28 (21.5)
Lying	0	0	0
Aggression	70 (35)	37 (52.9)	33 (25.4)

BDI-Ⅱ: Beck Depression Inventory (2nd edition); HAM-A: Hamilton Anxiety; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; EPQ-R: Eysenck Personality Questionnaire-Revised Rating Scale.

Table 3 Frequencies of psychiatric abnormalities in the studied group of epilepsy in relation to gender *n* (%)

Psychiatric disorders	Males (*n* = 100)		Females (*n* = 100)	
	Males with suicide (*n* = 34)	Males without suicide (*n* = 66)	Females with suicide (*n* = 36)	Females without suicide (*n* = 64)
BDI-Ⅱ	34 (100)	18 (27.27)	26 (72.22)	34 (53.13)
Mild	3 (8.82)	7 (38.89)	2 (7.69)	5 (14.71)
Moderate	10 (23.26)	5 (27.78)	8 (30.77)	14 (41.18)
Severe	17 (52.94)	6 (33.33)	16 (61.54)	15 (44.12)
HAM-A	27 (79.41)	15 (22.72)	24 (66.67)	30 (46.88)
Mild	4 (14.81)	3 (20)	3 (12.5)	9 (30)
Moderate	9 (33.33)	8 (53.33)	5 (20.83)	8 (26.67)
Severe	14 (51.85)	4 (26.67)	16 (66.67)	13 (43.33)
Y-BOCS	22 (64.71)	27 (40.91)	17 (47.22)	39 (60.94)
Mild	9 (40.91)	13 (48.15)	4 (23.53)	19 (48.72)
Moderate	4 (18.18)	7 (25.93)	3 (17.65)	13 (33.33)
Severe	4 (18.18)	4 (14.81)	7 (41.18)	3 (7.69)
Extreme	5 (22.73)	3 (11.11)	3 (17.65)	4 (10.26)
EPQ-R				
Psychosis	5 (14.7)	29 (43.9)	8 (22.4)	29 (45.3)
Neurosis	4 (11.8)	18 (27.3)	7 (19.4)	7 (19.4)
Extroversion	4 (11.8)	22 (33.3)	1 (2.8)	6 (9.4)
Lying	0	0	0	0
Aggression	20 (58.8)	21 (31.8)	17 (47.2)	12 (18.8)

BDI-Ⅱ: Beck Depression Inventory (2nd edition); HAM-A: Hamilton Anxiety; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; EPQ-R: Eysenck Personality Questionnaire-Revised Rating Scale.

Ⅱ ($P = 0.0001$), HAM-A ($P = 0.0001$) and Y-BOCS ($P = 0.037$) and lower concentrations of serotonin ($P = 0.006$), noradrenaline ($P = 0.019$) and adrenaline ($P = 0.0001$), while the latter group had lower scores of psychotic ($P = 0.0001$), neurotic ($P = 0.003$) and extroversion ($P = 0.025$) personality traits (Tables 6 and 7).

In presence of suicidality, significant correlations were identified between: (1) age and scores of BDI-Ⅱ ($r = 0.235$, $P = 0.0001$) and HAM-A ($r = 0.241$, $P = 0.046$); (2) age at onset and concentrations of noradrenaline ($r = -0.502$, $P = 0.024$); (3) duration of illness and scores of BDI-Ⅱ ($r = 0.247$, $P = 0.041$), Y-BOCS ($r = 0.270$, $P = 0.025$) and neurotic personality trait ($r = -0.284$, $P = 0.018$); and (4) doses of AEDs and scores of psychotic personality traits ($r = -0.495$, $P = 0.006$ for CBZ; $r = -0.508$, $P = 0.0001$ for VPA). In absence of suicidality, significant correlations were identified between: (1) age at onset and scores of BDI-Ⅱ ($r = 0.350$, $P = 0.043$) and serotonin concentrations ($r = -0.432$, $P = 0.014$); and (2) doses of AEDs and scores of psychotic ($r = -0.271$, $P = 0.020$) and neurotic ($r = -0.348$, $P = 0.003$) personality traits.

DISCUSSION

Several longitudinal and large sample-sized population studies with longer durations of follow-up, have shown that suicide is more frequent with epilepsy than in general population and represents the chief cause of death with epilepsy[3,4,6]. However, big differences in rates of suicidality have been shown across epilepsy studies. In this study, we reported high prevalence of suicidality (35% *vs* 9% for control subjects). In the literature, the estimated lifetime prevalence of suicide in epileptic population is 3.3%-14.3% or even up to 25%-32.5%[2,4] compared to 1.4%-6.9% for general population[5]. In contrast, some investigators did not find excess mortality with epilepsy due to suicide[28]. These great differences reflect the heterogeneity of epilepsy and epileptic disorders and differences in culture and risk factors across populations.

We and others reported a link between epilepsy, suicidality and comorbid interictal psychiatric abnormalities[4,9,29]. Depression was the most prevalent (80%) psychiatric comorbidity in patients with suicidality, followed by anxiety (72.86%), obsession (55.71%) and aggression (52.9%). Several studies reported that depression is the most prevalent interictal with epilepsy and frequently associated with emotional instability, poor impulse control, anxiety, obsession and aggression, reaching about 15%-18.9% or even as high as 50 times that of the general population[9,30,31]. Anxiety is the second most frequent psychiatric comorbiditiy with epilepsy and commonly associated with depression, inattention, aggression and obsession[32]. Obsession is the third most frequent psychiatric comorbiditiy with epilepsy and commonly associated with depression and anxiety, hostility, aggression, paranoid ideation, low intelligence, seizure frequency, duration of education, brain magnetic resonance imaging abnormalities and number of AEDs[33]. Male sex, increasing age, long duration of illness and lack of control on AEDs were the identified risks for higher scores of depression, anxiety and obsession[6,30,31]. It was observed that the earlier onset of seizures (< 18 years old), the better quality of life in adulthood. This reflects the more effective copying mechanisms and the adjustment to social and psychological consequences of the disease, while the late onset seizures, the more disruption of patient's life (e.g., due to loss of the ability to drive and unemployment)[34].

Table 4 Significance between patients and control subjects in scores of BDI-Ⅱ, HAM-A, Y-BOCs and EPQ-R in relation to epilepsy itself- and its treatment-related variables regardless to the presence or absence of suicidality

Epilepsy itself- and its treatment-related variables	BDI-Ⅱ	HAM-A	Y-BOCS	EPQ-R			
				Psychosis	Neurosis	Extroversion	Lying
Type of epilepsy							
Generalized							
P1	0.0001	0.296	0.003	0.015	0.0001	0.435	0.0001
Focal							
P1	0.0001	0.214	0.008	0.001	0.0001	0.436	0.0001
P2	0.511	0.958	0.682	0.729	0.521	0.867	0.786
Focal epilepsies							
Frontal							
P1	0.0001	0.182	0.001	0.005	0.0001	0.346	0.0001
Temporal							
P1	0.005	0.259	0.555	0.011	0.0001	0.448	0.0001
P3	0.514	0.607	0.037	0.818	0.656	0.893	0.353
Side of epileptic activity							
Right							
P1	0.0001	0.327	0.068	0.030	0.0001	0.131	0.002
Left							
P1	0.001	0.138	0.015	0.003	0.0001	0.821	0.0001
P4	0.919	0.697	0.805	0.800	0.397	0.189	0.064
CBZ							
P1	0.0001	0.852	0.007	0.0001	0.0001	0.407	0.0001
P5	0.857	0.186	0.900	0.071	0.897	0.682	0.242
P6	0.005	0.004	0.213	0.034	0.160	0.443	0.155
VPA							
P1	0.007	0.074	0.108	0.207	0.0001	0.762	0.0001
P6	0.024	0.112	0.279	0.750	0.299	0.341	0.039
Polytherapy							
P1	0.0001	0.003	0.003	0.380	0.0001	0.199	0.013
Controlled							
P1	0.714	0.001	0.144	0.0001	0.878	0.034	0.0001
P7	0.070	0.020	0.499	0.001	0.001	0.025	0.238
P8	0.0001	0.0001	0.087	0.0001	0.0001	0.0001	0.951
Partially uncontrolled							
P1	0.078	0.917	0.611	0.033	0.0001	0.992	0.0001
P8	0.0001	0.0001	0.010	0.183	0.034	0.017	0.176
Uncontrolled							
P1	0.0001	0.0001	0.0001	0.373	0.0001	0.007	0.0001

CBZ: Carbamazepine; VPA: Valproate; BDI-Ⅱ: Beck Depression Inventory (2nd edition); HAM-A: Hamilton Anxiety; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; EPQ-R: Eysenck Personality Questionnaire-Revised Rating Scale; P1: Patients *vs* controls; P2: Generalized *vs* focal; P3: *vs* frontal; P4: Right *vs* left; P5: CBZ *vs* VPA; P6: *vs* polytherapy; P7: *vs* partially controlled; P8: *vs* uncontrolled.

It seems that the increase in the prevalence of suicidality with comorbid depression, anxiety and obsession in patients with epilepsy is due to the followings: (1) poor adjustment to seizures occur as a result of low socio-economic status, financial stress and poor cultural approach to epilepsy, the lower the expectations of parents and teachers, poor academic achievement, unemployment, inability to drive and diminished sexual desire and marital stresses. All result in low self-esteem, social isolation, stigmatization, depression, low quality of life and increase the risk of suicidality with epilepsy[34]; (2) misinformation about the disorder, results in low self-esteem, stigmatization, restrictions of normal daily activites, depression, obsessions, anxiety and increase the risk of suicidality with epilepsy[32]; and (3) giving in to obsessions and compulsions, knowing that they are unreal and incapacity to stop them, result in lack of self-confidence, depression, anxiety and even suicide[33].

We and others[35] observed no difference in the prevalence of suicidality and scores of psychiatric questionnaires and scales in relation to the dose, drug level and duration of treatment with AEDs. This indicates that the impact of epilepsy itself on suicidality is more significant than its medications. In contrast, suicidality was found in 4.3/1000 patients treated with AEDs in the active arm, compared with 2.2 per 1000 patients in the comparison arm as a result of a meta-analysis done by the Food and Drug Administration (FDA) on 199 randomized clinical trials and encompassed on 43 892 patients treated with different 11 AEDs for epilepsy, psychiatric disorders, pain and others. Which were: CBZ, VPA, felbamate, gabapentin, lamotrigine, levetracitam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide. Thus, in January 2008 and based on this meta-analysis, FDA reported that exposure to AEDs increased the risk of suicidality by 1.80-fold. The FDA issued an alert and decided to insert

Table 5 Significance between patients and control subjects in the concentrations of serotonin, catecholamines and dopamine in relation to epilepsy itself- and its treatment-related variables regardless to the presence or absence of suicidality

Epilepsy-related variables	Serotonin	Noradrenaline	Adrenaline	Dopamine
Type of epilepsy				
Generalized				
P1	0.002	0.016	0.0001	0.051
Focal				
P1	0.017	0.007	0.0001	0.558
P2	0.176	0.305	0.662	0.096
Focal epilepsies				
Frontal				
P1	0.074	0.032	0.0001	0.469
Temporal				
P1	0.003	0.014	0.0001	0.400
P3	0.375	0.575	0.818	0.810
Side of epileptic activity				
Right				
P1	0.031	0.061	0.0001	0.754
Left				
P1	0.017	0.007	0.0001	0.387
P4	0.781	0.392	0.966	0.626
CBZ				
P1	0.068	0.001	0.0001	0.064
P5	0.239	0.546	0.682	0.739
P6	0.051	0.374	0.682	0.528
VPA				
P1	0.009	0.007	0.0001	0.324
P6	0.170	0.628	0.698	0.867
Polytherapy				
P1	0.007	0.243	0.0001	0.806
Controlled				
P1	0.136	0.115	0.0001	0.208
P7	0.189	0.116	0.090	0.056
P8	0.185	0.174	0.528	0.683
Partially uncontrolled				
P1	0.019	0.003	0.0001	0.542
P8	0.903	0.524	0.158	0.034
Uncontrolled				
P1	0.012	0.001	0.0001	0.004

CBZ: Carbamazepine; VPA: Valproate; P1: Patients *vs* controls; P2: Generalized *vs* focal; P3: *vs* frontal; P4: Right *vs* left; P5: CBZ *vs* VPA; P6: *vs* polytherapy; P7: *vs* partially controlled; P8: *vs* uncontrolled.

suicide warnings in the package inserts of all AEDs[10]. However, the results of FDA meta-analysis must be considered with caution because of the followings[36]. (1) not all patients with epilepsy but some of them may be more susceptible to negative psychotropic effect of AEDs which may be resulted from the direct (i.e., anticonvulsant mechanisms) and/or the indirect effect of the AEDs as: (a) metaboolic adverse effects (folate deficiency); (b) interactions between the AED and the underlying epileptic process; (c) presence of hippocampal sclerosis; (d) forced normalization; (e) polytherapy; and (f) past or family history of psychiatric disorder; and (2) some AEDs (e.g., CBZ, VPA, topiramate and gabapentin) are well known mood stabilizers and are used in treatment of bipolar, impulse-control, borderline personality and episodic dyscontrol disorders. Thus patients with epilepsy should be closely followed whenever a new AED is introduced.

To summarize, it seems that the comorbidity between suicidality and epilepsy is correlated to epilepsy itself-related clinical, psychosocial and biological variables and not to its medications (AEDs). This is supported by the findings of this and other studies as follow: (1) the frequency of suicidality was associated with increase in seizures' frequency, severity of seizures and intractability to medications. On the other hand, the frequency of depression and suicidality was associated with the type of epilepsy (e.g., GTC and frontal and temporal lobe epilepsies[37] and the lateralized foci of epileptic activity[38]; (2) lower blood concentrations of serotonin and catecholamines were identified in patients regardless to the presence or absence of suicidality[39,40]; (3) some investigators observed the followings: (a) the absence of a correlation between the severity of seizures and depression; (b) seizure-free state couldn't protect patients from developing depression and consequently suicide; (c) improvement of psychiatric manifestations with disappearance of seizures after temporal lobectomy[41]; and (d) In fact: (i) some brain areas and their connections are incriminated in generating both epileptic discharges and psychiatric symptoms which include: frontal-limbic-

Table 6 Comparative statistics between patients with and without suicidality and control subjects in relation to psychosocial variables

	BDI-Ⅱ	HAM-A	Y-BOCS	EPQ-R			
				Psychosis	Neurosis	Extroversion	Lying
Patients with history of suicidality (n = 70)							
Range	3.0-53.0	3.0-44.0	0.0-38.0	3.00-20.00	4.0-21.00	3.0-18.0	3.0-18.0
Mean	27.19	21.30	14.25	8.94	11.56	9.83	11.14
25th Percentiles	18.00	12.75	4.00	6.00	8.00	6.00	8.75
50th Percentiles	26.50	22.00	13.50	9.00	10.50	9.00	11.00
75th Percentiles	37.25	28.25	24.25	11.00	13.25	15.00	13.25
Patients without history of suicidality (n = 130)							
Range	1.0-50.0	1.0-44.0	0.0-40.0	3.0-15.0	4.00-21.00	2.0-18.0	2.0-19.0
Mean	15.88	11.95	10.72	11.65	13.42	11.38	11.00
25th Percentiles	7.00	5.00	2.00	4.00	9.00	17.00	9.00
50th Percentiles	11.00	8.00	9.50	6.00	13.00	13.00	11.00
75th Percentiles	23.25	18.00	16.00	9.00	18.00	16.00	13.00
Control subjects (n = 100)							
Range	1.0-51.0	2.0-48.0	0.0-35.0	2.0-13.0	3.0-22.0	2.0-19.0	3.0-18.0
Mean	11.80	13.20	7.54	6.50	18.08	11.27	8.47
25th Percentiles	7.00	6.00	2.25	4.00	14.00	6.25	7.00
50th Percentiles	10.00	10.50	6.00	7.00	18.00	12.00	9.00
75th Percentiles	14.00	15.00	12.00	9.00	19.75	16.75	10.00
Significance							
P1	0.0001	0.0001	0.0001	0.0001	0.0001	0.050	0.0001
P2	0.031	0.235	0.042	0.0001	0.0001	0.108	0.0001
P3	0.0001	0.0001	0.037	0.750	0.003	0.025	0.911

BDI-Ⅱ: Beck Depression Inventory (2nd edition); HAM-A: Hamilton Anxiety; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; EPQ-R: Eysenck Personality Questionnaire-Revised Rating Scale; P1: Patients with suicide *vs* control subjects; P2: Patients without suicide *vs* control subjects; P3: Patients with suicide *vs* patients without suicide.

Table 7 Comparative statistics between patients with and without history of suicide and control subjects in relation to concentrations of serotonin, catecholamines and dopamine

	Serotonin (ng/mL)	Noradrenaline (ng/mL)	Adrenaline (ng/mL)	Dopamine (ng/mL)
Patients with history of suicidality (n = 70)				
Range	0.00-96.3	1.1-161.5	0.10-80.2	0.10-165 222
Mean	36.25	40.27	8.60	9133.12
25th Percentiles	10.70	4.13	4.10	14.03
50th Percentiles	21.40	20.90	5.10	51.85
75th Percentiles	64.20	61.25	60.35	837.98
Patients without history of suicidality (n = 130)				
Range	0.0-96.30	2.0-213.4	0.10-521.40	0.10-2145.00
Mean	42.67	57.53	27.71	301.44
25th Percentiles	21.60	4.70	0.10	5.50
50th Percentiles	42.80	30.65	0.10	34.00
75th Percentiles	64.20	104.35	4.08	161.50
Control subjects (n = 100)				
Range	42.8-107.0	1.50-493.20	0.1-1914.00	0.10-5146.0
Mean	71.69	125.35	314.72	235.53
25th Percentiles	50.83	28.30	9.85	20.50
50th Percentiles	69.55	128.00	55.00	56.60
75th Percentiles	96.30	181.50	417.45	6253.80
Significance				
P1	0.031	0.005	0.0001	0.282
P2	0.006	0.019	0.0001	0.077
P3	0.303	0.399	0.719	0.842

P1: Patients with suicide *vs* control subjects; P2: Patients without suicide *vs* control subjects; P3: Patients with suicide *vs* patients without suicide.

subcortical circuits, frontal-striatal systems and limbic-brainstem, amygdale-hypothalamic and amygdale-locus coeruleus connections[37,38,42-44]; and (ii) disturbances in serotonin metabolism has been found by many investigators to be involved in the pathogenesis of suicide irrespective of primary diagnosis. Thus Serotonin could be a link between suicidality, epilepsy, depression, anxiety and obsession[45].

In conclusion, this is the first study in our population which systematically estimated the prevalence and risks of suicidality in a homogenous group of patients with epilepsy. This study emphasizes the importance of epilepsy itself as a risk for suicidality and not its treatment. Thus, early recognition of seizures, optimizing seizure control and managing its comorbid psychiatric symptomatology and disorders are of paramount importance while managing patients with epilepsy (i.e., biopsychosocial model of treatment which focuses on the whole person rather than simply treating convulsions). However and despite the importance of this study, its main limitation is that the majorities of patients had chronic and severe illness and were intractable to medications. This can be explained by the fact that patients were recruited from a University Hopital (a tertiary referral hospital). Thus performing multicenter studies will represent the accurate prevalence of suicidality with epilepsy of different severities.

COMMENTS

Background

Epilepsy is a common chronic medical problem with a prevalence rate of 8.2-12.9 per 1000 in general population. Suicidality with epilepsy (suicidal thoughts and attempts) is a common cause of mortality with epilepsy which accounts for > 10% of deaths from epilepsy compared with 1.4% in general population. Its lifetime prevalence has been estimated to be between 3.3%-32.5% compared to 1.4%-6.9% in general population. The great difference in prevalence of suicidality between studies might reflect the heterogeneity of epilepsy and epileptic disorders and the differences in risks, study designs and studied populations. The risk factors of suicidality with epilepsy are multiple and include: male sex, early age of onset, severe epilepsy, generalized tonic-clonic convulsions, temporal lobe epilepsy, polymorphic seizures combination, lateralization of epileptic activity, absence of seizures for a long time especially after being very frequent, recent control of seizures, cognitive deterioration and psychiatric comorbidity. The majority (81%-100%) of suicides occurs in subjects with psychiatric abnormalities as depression (which is the most common with a risk of 15%-18.9%), anxiety, epileptoid personality, past or family histories of psychiatric disorders and/or suicidal attempts. Recently, antiepileptic drugs (AEDs) have been suggested as a risk of suicide in patients with epilepsy.

Research frontiers

Suicidality (suicidal thoughts and attempts) is a common risk of morbidity and mortality in patients with epilepsy. The research hotspot is to identify the difference in risk variables (e.g., epilepsy itself- and its treatment-related factors) in different populations as there is great difference in the prevalence of suicidality with epilepsy across studies. Early recognition and possible modification of such variables will have a positive impact on medical management and quality of life with epilepsy.

Innovations and breakthroughs

This is the first study which systematically estimated the prevalence and risk variables of suicidality in a homogenous group of patients with epilepsy. A clinical psychiatric interview, a comprehensive battery of psychiatric questionaires and scales and blood concentrations of serotonin, catecholamines and dopamine (i.e., neurochemicals which link epilepsy, psychiatric abnormalities and suicidality) were used for analyses. In this study, we reported that epilepsy itself and not its medications is incriminated as a risk for suicidality.

Applications

While managing patients with epilepsy, the responsible physicians have to optimize seizure control and manage the comorbid psychiatric symptoms and disorders.

Terminology

A seizure is defined as a clinical phenomena resulting from brief hyperexcitability of the cerebral hemispheric neurons. Epilepsy is a recurrent unprovoked seizures (≥ 2) and manifested according to the disturbaned brain area (e.g., disturbance of consciousness, behavior, emotion, motor function, sensation or autonomic manifestations). The cause of epilepsy is usually primary (idiopathic) or secondary to severe brain insult (symptomatic epilepsy). AEDs are currently the mainstay for treatment of epilepsy. The known mechanisms of action of AEDs are: (1) sodium, calcium and potassium channels blockades; (2) enhancement of GABAergic activity; (3) decrement in glutamate-mediated excitation; and (4) others. The majority of patients become seizure free after 2-5 years and utilization of AEDs and thus the AEDs can be slowly discontinued. Some types of epilepsy (20%-35%) are difficult to control for a significant period of time even with addition of 2nd or 3rd AED (conventional or new) (medically intractable). The risks of recurrent brief seizures, intractability and the adverse effects from chronic medications may result in medical, metabolic, neuroendocrinal, cognitive and psychiatric problems. Sometimes, psychiatric symptoms (e.g., major depression, generalized anxiety disorder, psychosis, obcessive-compulsive disorder, aggression and suicide) are enduring and negatively impact patient's quality of life. The exact mechanisms of comorbid psychiatric abnormalities are complex and poorly understood, however, clinical-, psychosocial- and treatment- related variables are considered as the main risks.

Peer review

The risks of suicidality in adult patients with epilepsy is an interesting original study on the prevalence and clinical correlates of suicidality in patients with epilepsy. The sample size is adequate and the biochemical tests are an added value to the study.

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Events Calendar 2012

January 19-22, 2012
The 64th Annual National Congress of The Indian Psychiatric Society
Kochi, Kerala, India

January 20-21, 2012
AACAP 2012 Psychopharmacology Update Institute
Child and Adolescent Psychopharmacology: Integrating Current Data into Clinical Practice
Sheraton New York Hotel and Towers, New York, United States

Februrary 08-11, 2012
Thematic Conference of the World Psychiatric Association
Granada

Februrary 09-10, 2012
14th National Conference: Dementias 2012
London, United Kingdom

February 9-12, 2012
New Zealand Association of Psychotherapists Conference 2012
The Face of the Other
Victoria University, Wellington, New Zealand

February 18, 2012
Inaugural RANZCP Symposium on Youth Mental Health
Mantra on Russell, Melbourne, Australia

Februrary 23-24, 2012
Ⅱ Annual Meeting on Therapeutics in Psychiatry
Barcelona, Italy

February 23-24, 2012
Voices VIC 2012 Conference
Voices, Conversations & Transformations – Diverse Approaches to Recovery
Storey Hall, RMIT University, Melbourne, Australia

February 23-25, 2012
American Psychosocial Oncology Society 9th Annual Conference
Miami, FL, United States

February 29, 2012
Conjoint Medical Education Seminar
Hilton on the Park, Melbourne, Australia

March 3-6, 2012
20th European Congress of Psychiatry
Prague, Czech Republic

March 16-19, 2012
2012 American Association for Geriatric Psychiatry Annual Meeting
Washington, DC, United States

March 17, 2012
Body In Mind 2012
AMREP Centre, Alfred Hospital, Melbourne, Australia

March 21-24, 2012
American Neuropsychiatric Association 23rd Annual Meeting
New Orleans, LA, United States

March 21-25, 2012
American Counseling Association 2012 Annual Conference & Exposition
San Francisco, CA, United States

March 23-24, 2012
Psychiatric Society of Virginia 2012 Spring Meeting
Richmond, VA, United States

March 27-31, 2012
5th Annual Psychopharmacology Institute and ISPN Annual Conference - International Society Of Psychiatric-Mental Health Nurses
Atlanta, GA, United States

April 11-14, 2012
33rd Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine
New Orleans, LA, United States

April 12-15, 2012
2012 Anxiety Disorders Association of America Annual Conference
Arlington, VA, United States

April 16-18, 2012
Australian & New Zealand Disaster and Emergency Management Conference
Brisbane Convention Centre, Australia

April 18-21, 2012
45th American Association of Suicidology Annual Conference
Baltimore, MD, United States

April 23-26
Freedom and Recovery: Integrated Mental Health and Addiction Treatment for Service Members
San Diego, CA, United States

May 2-4, 2012
ANZSGM Annual Scientific Meeting 2012
Dementia: Managing Not to Forget
Hilton Hotel, Sydney, Australia

May 5-9, 2012
2012 American Psychiatric Association Annual Meeting
Philadelphia, PA, United State

May 20-24, 2012
RANZCP 2012 Congress
Hobart, Tasmania, Australia

June 14-17, 2012
American Psychiatric Nurses Association 9th Annual Psychopharmacology Institute
Reston, VA, United States

July 6-8, 2012
RANZCP Queensland Branch Weekend Conference
Hyatt Regency Coolum, Australia

July 7-10, 2012
Society For Developmental and Behavioral Pediatrics 2012 Annual Meeting
Phoenix, AZ, United States

July 10-13, 2012
International Congress of the Royal College of Psychiatrists
BT Convention Centre, Liverpool, United Kingdom

August 6-8, 2012
13th International Mental Health Conference
Outrigger Inn, Gold Coast, Australia

September 4-7, 2012
Faculty of Forensic Psychiatry Conference
Hong Kong Academy of Medicine, Hong Kong, China

September 7-11, 2012
International Psychogeriatric Association International Meeting 2012 (Jointly Hosted By the RANZCP Faculty of Psychiatry of Old Age)
Cairns, Queensland, Australia

September 13-16, 2012
American Association For Marriage And Family Therapy Annual Conference 2012
Charlotte, NC, United States

September 27-29, 2012
2nd International Congress on Borderline Personality Disorder and Allied Disorders
Match research, need and demand to treatment and resources
RAI Amsterdam, The Netherlands

October 1-3, 2012
Ranzcp Section of Psychotherapy 2012 Conference
Monash University Centre, Prato, Italy

October 3-5, 2012
RANZCP Faculty of Child and Adolescent Psychiatry Annual Meeting
Novotel Manly Pacific, Sydney, Australia

October 4-7, 2012
64th Institute On Psychiatric Services
New York, NY, United States

October 13-14, 2012
RANZCP Victorian Branch Conference 2012
RACV Healesville Country Club, Australia

October 17-20, 2012
International Convention Of Pan-American Medical Women´s Alliance
Guadalajara, Mexico

October 21-24, 2012
ISQua 29th International Conference
Geneva, Switzerland

November 7-10, 2012
American Psychiatric Nurses Association 26th Annual Conference
Pittsburgh, PA, United States

November 8-11, 2012
International Conference on Clinical Practice in Alzheimer Disease
Budapest, Hungary

November 20-23, 2012
Silent Witnesses: The Place of Coronial System in A Civilised Society (Asia Pacific Coroners' Society)
Amora Hotel, Sydney, Australia

November 22-25, 2012
The 2nd International Multidisciplinary Forum on Palliative Care
Florence, Italy

November 10-12, 2012
CHADD 23rd Annual International Conference on ADHD - Children and Adults with Attention Deficit/Hyperactivity Disorder
Lake Buena Vista, FL, United States

WJP World Journal of Psychiatry

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GENERAL INFORMATION

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The columns in the issues of *WJP* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in psychiatry; (8) Brief Articles: To briefly report the novel and innovative findings in psychiatry; (9) Case Report: To report a rare or atypical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJP*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of psychiatry; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in psychiatry.

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2220-3206/g_info_20100725072755.htm.

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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