Introduction
Depression is common in patients with epilepsy, resulting in lack of response to antiepileptic drugs. Antiepileptic drugs are found to reduce folic acid level. Depression is a common symptom of folate deficiency. This study was undertaken to assess the relationship between serum folate levels and depression in patients with refractory epilepsy.

Patients and Methods
The study included 37 patients with refractory epilepsy, attending the neuropsychiatric outpatient clinic in the Suez Canal University hospital after giving written informed consent. We included adult male and female patients with age ranging from 18–40 years. Patients were subjected to clinical history, examination, serum folate level, and Hamilton Depression Rating Scale.

Results
According to the Hamilton Depression Scale, 62.2% were estimated to have mild, moderate, and severe depression. Half of the patients (48.7%) were estimated to have low levels of folic acid, with nine of them (24.3%) having low normal values. There was significant association between severe depression and low folic acid level (<3.5). Longer duration of the disease was found to be associated with lower folic acid levels and higher depression scale score with significant difference. There was no significant association between received drugs and the severity of depression or low serum folic acid.

Conclusion
Depression was higher in patients with refractory epilepsy. Low serum folic acid was considered as a risk factor for depression and its severity in patients with refractory epilepsy, particularly in patients receiving polytherapy.

Keywords:
depression, folic acid, refractory epilepsy

Patients and methods
The study included 37 patients with refractory epilepsy attending the neuropsychiatric outpatient clinic in Suez Canal University hospital after giving written informed consent. Both adult male and female patients with age ranging from 18 to 40 years old were included. We excluded patients who did not experience epileptic seizures for at least 2 weeks, patients receiving folic acid supplementation, patients known to be mentally retarded, patients with psychotic symptoms, patients with chronic organic diseases, patients with family history of depression, patients with substance abuse, and female patients in premenstrual or postmenopausal periods.

Patients fulfilling the inclusion and exclusion criteria were subjected to clinical history, examination, serum
folate level in which the normal range of folate levels is 3.5–16.1 ng/ml (3.5 ng/ml–7.7 ng/ml will be considered to be in the low normal range) [8], and the Hamilton Depression Rating Scale in which a multiple-choice questionnaire was used to detect and to rate the severity of a patient’s depression [9].

Data were imported into the Statistical Package for the Social Sciences (latest available version of SPSS, SPSS Inc., Chicago, Illinois, USA) software for analysis. According to the type of data, the following tests were used to test differences for significance: $\chi^2$ and paired t-test. The assessment of odds ratio was used to test the relationship between different dependent and independent variables. $P$ value was set at a value of less than 0.05 for significant results and less than 0.01 for highly significant results. An informed consent was taken from all the patients before taking any data or conducting any investigations.

Results
Of the 37 patients, 20 of them (54.1%) were women and 17 of them (45.9%) were men. The age of the studied patients was found to be ranging from 22 to 38 years.

According to the received medications and duration of disease, no monotherapy was received, most commonly drugs were used in combination (polytherapy) of two or three drugs. Carbamazepine and phenytoin were received by 28 patients for each drug (75.7%). Valporic acid was received by 24 patients (64.8%). The mean duration of the disease was 12.1 years with most of the patients (56.8%) having been diagnosed for 10–15 years.

According to the Hamilton Depression Scale, 14 patients (37.8%) were not depressed. Ten patients (27.1%) were estimated to have mild depression, whereas eight (21.6%) had severe depression (Table 1).

Approximately half of the patients (48.7%) were estimated to have low levels of folic acid, with nine of them (24.3%) having low normal values (Table 2). There was no significant association between received drugs and the severity of depression. However, most of the patients with severe depression were receiving carbamazepine and phenytoin as part of their therapy, either alone or in combination with valporic acid (Table 6). There was also no significant association between received drugs and low serum folic acid, although most of the patients with low serum folic acid were receiving carbamazepine and phenytoin as part of their therapy, either alone or in combination with valporic acid (Table 7).

Table 2 Folic acid level among the studied patients

<table>
<thead>
<tr>
<th>Folic acid level</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;3.5)</td>
<td>18</td>
<td>48.7</td>
</tr>
<tr>
<td>Low normal (3.5–7.7)</td>
<td>9</td>
<td>24.3</td>
</tr>
<tr>
<td>Medium normal (7.8–11.9)</td>
<td>5</td>
<td>13.5</td>
</tr>
<tr>
<td>High normal (12–16)</td>
<td>5</td>
<td>13.5</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>100</td>
</tr>
</tbody>
</table>

Discussion
Depression is the most common psychiatric disease in patients with epilepsy [1]. An average incidence of 30–40% is, however, assumed [10]. Hiitiris et al. [2] reported that depression due to the reduction in serum folate, which is associated with the induction of enzymes by AEDs, has been associated with lack of response to AEDs and thereby with the likelihood of developing pharmacoresistant epilepsy.

Hence, more important is that if the depression is not detected the epilepsy is actually harder to control, again probably for biological reasons [11]. Schuele and Lüders [12] found that emotional and psychosocial difficulties are disproportionately high in people with refractory epilepsy.

In this study, the prevalence of depression among the studied patients with refractory epilepsy was found to be 62.2%. This finding agrees with the findings by Gilliam et al. [13], Victoroff et al. [14], and Jones et al. [15], as they reported that 50–58% of the patients with refractory epilepsy were identified as having depression. O’Donoghue et al. [16] also noted that depression occurred more frequently in patients with higher seizure frequency compared with seizure-free patients.

In contrast, Attarian et al. [17] reported that patients with epilepsy have a higher prevalence of depression than the general population, but the intractability of the seizure disorder does not seem to be an independent risk factor for the occurrence of depression. This contrast may be due to using of the Beck Depression Inventory in that study to evaluate depressive symptoms. Depression in epilepsy is multifactorial in nature and has been shown to be influenced by a number of factors, which includes neurobiological, psychosocial, and pharmacological factors [18].

In this study, 48.7% were estimated to have low levels of folic acid (<3.5), in addition to 24.3% having low normal values (3.5–7.7 ng/ml). This finding is agreed with Hermann et al. [19] as they found in 46 patients with chronic epilepsy.
Folate serum level was below the normal range limit in 21.7% of patients with chronic epilepsy, of the remaining patients 45.6% had a low normal folate level. In this study, there was significant association between depression and low serum folic acid level. Fifteen (40.5%) of the studied patients were found to have depression (ranging from mild, moderate, and severe depression) and low folic acid level (< 3.5). Seven (18.9%) of the studied patients were found to have severe depression and low folic acid level (< 3.5). Most of the patients with no depression (29.7%) were estimated to have normal levels of folate acid (ranging from low normal to high normal levels) and 13.5% of the patients with no depression were estimated to have high normal level of folate acid, which was a statistically significant difference.

This agreed with the findings by and Froscher et al. [20], who reported that in patients with psychiatric disorders, patients with epilepsy have a lower folate serum level than controls, and Kishi et al. [21] found that the reduction in serum folate is associated with the induction of enzymes by AEDs. Hermann and Whitman [22] in their study found that patients with minor depression had a significantly lower serum folate level than patients without depression.

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In this study, longer duration of the disease was found to be associated with higher depression scale score. The mean duration of the disease was 12.1 years with most of the patients having been diagnosed for 10–15 years now (56.8%). This finding is consistent with most of the studies that found correlation between seizure frequency, longer duration of epilepsy, and depression [17,23]. This is in contrast with Glosser et al. [24], Oguz et al. [25], Baki et al. [26], and Kim et al. [27] who found that, however, the age, age of onset, duration of illness, religion, education, and multidrug therapy were not related to the severity of depression. The reasons for inconsistencies between these results and other studies are possibly due to differences in study groups, as other studies evaluate temporal lobe epileptic patients with hippocampal atrophy or hippocampal sclerosis, whereas this study evaluated patients with refractory epilepsy and used a different scale for evaluating depression.

In present study, there is no monotherapy was received, most commonly drugs were used in combination (polytherapy) of two or three of drugs among the studied patients, were carbamezapine and phenytoin were received by twenty eight of the patients for each drug (75.7%). Valproic acid was received by 24 patients (54.1%). This finding is nearly similar to the study conducted by Meneses et al. [28], who found that the most frequently used AEDs were phenytoin, valproic acid, carbamazepine, clozazapam, and primidone.

In this study, there was no significant association between received drugs and the severity of depression. However, most of the patients with severe depression were receiving carbamezapine and phenytoin as part of their therapy either alone or in combination with valproic acid. This finding agrees with the study by Meneses et al. [28] and Mensah et al. [29], as they reported that depression was not associated with monotherapy or polytherapy. In contrast, Nemeroff and Owens [4] reported that carbamazepine, phenobarbital, phenytoin, and vigabatrin can contribute to depression and memory impairment.

Ogawa et al. [6] found that some AEDs are at risk for low levels of serum and red blood cell folic acid. This finding is in contrast to this study as there was no significant association between received drugs and the low serum folic acid. However, most of the patients with low serum folic acid were receiving carbamezapine and phenytoin as part of their therapy, either alone or in combination with valproic acid.

There is no conflict of interest to declare.

References
5 Van Praag HM, De Kloet ER, Van Os J. Stress, the brain and depression. Cambridge University Press; 2004.
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The association between low folic acid level and the development of epilepsy

The study aimed to investigate the association between low folic acid level and the development of epilepsy. A cross-sectional study was conducted to compare the levels of folic acid in patients with epilepsy and healthy controls. The results showed a significant difference in folic acid levels between the two groups. Low folic acid level was found to be associated with an increased risk of developing epilepsy. The study also highlighted the importance of folic acid supplementation in the management of epilepsy. Further research is needed to confirm these findings and explore the mechanisms underlying this association.