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Contents

Editorial.....IX

Gaye Hafez

Letter to Editor1

Eriona Heta

Research Article

Evaluation of Antidepressant Medication Use and Determination of Risk Factors for Depression among University Students in Istanbul3-18

Ecem Yıldız, Nilay Aksoy, Rashida Umar

The Burden of Care and Coping Strategies of Caregivers of Elderly Patients..... 19-32

Şerife Köleoğlu, Sevgin Samancıoğlu Bağlama

Review

A New Approach in Epilepsy Treatment: Nano-Carrier Systems 33-44

Burçak Yavuz, Özlem Yıldırım, Ahsen Gülizar Yılmaz

Industry 4.0 Elements for Pharmaceutical Development and Manufacture45-50

Buket Aksu, Gizem Yeğen

Instruction for Authors.....51-56

Editorial

Post-Covid Era

When we look back at this more-than-one-year period, we see that we have passed through a dust cloud. Although that cloud has not disappeared yet, we are now more hopeful with the help of ongoing vaccination all over the world. In this era where everything is changing so fast, it is also necessary to think about what awaits us with the end of the pandemic. How will the post-Covid era be shaped? There is a wide range of topics waiting to be discussed: the future of online education, management of health services, virtual and hybrid congresses, digitalization in every area, the necessity of managing financial resources to science and protecting nature. Emphasizing the vital importance of science is one of the areas that fundamentally interests us as scientists. The pandemic has reminded us once again that science is the only way out of such catastrophic events. The importance of investing in basic sciences was once again emphasized. Thinking about these multi-dimensional issues is as important as doing science, for this we should write articles and share ideas about the development and importance of scientific thinking in our journal.

As Aurum Journal of Health Sciences, we are pleased to announce our new issue. We would like to thank all writers and reviewers for their valuable contributions.

Gaye Hafez, PhD 

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Letter to Editor

22.12.2020

Dear Editor,

On October 7th, we got the news on Nobel Prize in Chemistry, awarded for CRISPR-Cas9 genetic scissors, the so-called game changer technology, which was first described in 2012. The prize was given to Emmanuelle Charpentier, director of the Max Planck Unit for the Science of Pathogens, in Berlin, Germany and Jennifer A. Doudna, professor at UC Berkeley and faculty scientist at Howard Hughes Medical Institute. The "First-all Female Scientists Team" promoted a huge development in science and opened doors to new discoveries in basic science, agriculture and medicine.

CRISPR-Cas9 gene editing tool has been adapted to a genome editing system that occurs naturally in bacteria. The bacteria create the so called CRISPR arrays, by capturing fragments of DNA from invading viruses. Via these arrays, the bacteria remember the virus and/or similar fragments of the virus. CRISPR-Cas9 technique has been worldwide used by researchers to develop new crops that withstand drought and pests, clinical trials for curing cancer, and there are hopes to help cure inherited diseases.

The recent achievements clearly show that humankind is benefiting from this technology. In clinical trials, some preliminary results showed that the altered genome of immune cells of three cancer patients has been well-tolerated and this could provide evidence of safety and feasibility in using CRISPR-Cas9 in treating human diseases. However, announcements like the birth of twin girls from genome edited embryos in November 2018 in China, raise up ethical, social, safety and efficacy concerns. Despite the main aim of the genome editing experimental trials being to fix genes with defects or make other edits in the genome of the embryo, it has been shown that unwanted changes of the genes can be generated. As a consequence, these changes lead to different outcomes in the cells of the same embryo. Such examples lead the scientific societies to conclusions, that the genome editing technology is not ready to be used in human embryos.

The countless applications are benefiting all of us in our research centres and we will most probably continue to benefit from this technology in the future. The number of CRISPR gene editing studies entering clinical trials is rapidly evolving for the treatment of various diseases. The first clinical trials in cancer patients involve the use of CRISPR-engineered T cells for cancer immunotherapy treatment with results supporting the effectiveness and general safety. Recent publications show early success of using genome editing tools to treat sickle-cell anaemia and β -thalassaemia. The *BCL11A* erythroid-specific enhancer was successfully targeted by CRISPR-Cas9.

There are still questions that need to be answered: what will happen with the human genome editing in the long run? When will genome editing be proven to be safe and efficient to be used in editing human embryos? How many more experiments are necessary to be done on embryos to get an answer? Are there going to be rules and authorization in using gene-therapy kits in human genome editing, to

prevent misuse of the technology? When will CRISPR-based gene editing be routinely used in clinic? We still need more time to get an answer to these questions and learn more about this technology. Let's see together what surprising outcomes genome editing science CRISPR-Cas9 will bring us.

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Research Article

Evaluation of Antidepressant Medication Use and Determination of Risk Factors for Depression among University Students in IstanbulEcem Yıldız¹ , Nilay Aksoy¹ , Rashida Umar² ¹Department of Clinical Pharmacy, Altınbaş University, Istanbul, Turkey, ²Department of Clinical Pharmacy, Faculty of Pharmacy, Medipol University, Istanbul, Turkey.

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Abstract: Depression is one of the most common mental health illnesses that can get worse without proper medical interventions. Estimates of the depression prevalence among university students occupy a fair portion of the general depressed populations. This study aimed to assess the prevalence of depression among university students and identifying their characteristics. The conducted cross-sectional study obtained data from different schools located in Istanbul. The highest participation in the study was from Altınbaş, Istanbul, Yeni Yüzyıl and İstinye Universities. The other universities are Yeditepe, Maltepe, Biruni, Istanbul Technical, Yıldız Technical, Bezmialem, Istanbul Kültür, Beykent and Marmara Universities. This study was conducted between December 2019 and March 2020 after the ethical committee approval. A total of 286 students were included in the study. 75% were female and the mean age and standard deviation (SD) of the students was 21.79 ± 1.775 years. Based on 'Beck Depression Inventory', the depressive state was observed to be no or minimal in 59%, mild in 20%, moderate in 16%, and severe in 5% of the participants. The student-related factors, such as the type of the school, cultural-social-financial issues were among the most factors that affect the incidence of depression in students. The students included in this study had only few information about depression and antidepressants which is not enough to understand the whole concept of depression and antidepressants.

Keywords: *Depression; anxiety; antidepressant; university students; Beck Depression Inventory*

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1. Introduction

Our modern technological lifestyle is indeed a transit card to enter a lot of unexpected mental problems such as dissatisfaction, being overfed, malnourished, sedentary, and socially isolated. Changes of this sort in

human lifestyle contribute to poor physical health and affect the incidence of depression which was defined in the latter days as a disease of modernity (Korkmaz, 2006). More than 264 million people, in other words 4.3% of the world population, suffer from depression. These alarming numbers reflect the wider prevalence of mental ill-health more generally. In a survey of 25,916 people in 15 different countries including Turkey, depression and anxiety were the most prevalent psychiatric conditions (James et al., 2018; Sartorius et al., 1996).

University students are susceptible to depression due to potential factors such as the accompanying stress to get high marks, fear from taking the adulthood responsibilities, finances, or possibly feeling isolated after moving away from friends and family. All these factors can lead to anxiety and behavioral disturbances (Buchanan, 2012; Hür et al., 2014). Depression that develops in this early stage of life can have a negative influence on an individual's career and social life. Studies have shown that depression in college students influences their study habits, self-acceptance, and cognitive performance as well as it has been associated with poor academic achievement, relationship discord, suicidal thoughts, and reduced productivity (Ibrahim et al., 2013; Newman et al., 1996). A study in United States has concluded that 447 out of 1338 undergraduate students reported problems during their childhood (such as financial difficulties, parental divorce, or orphan) as the main contributor to depression (Newhart et al., 2019).

Although psychosocial intervention is the first treatment method to treat minor depression symptoms, antidepressant drug use is increasing among university students without having enough information about the whole concept of depression, antidepressant, how these drugs work, and the adherence necessity with this type of drugs to get the full utility of them (Hammonds et al., 2015; Maruf et al., 2019). Different antidepressants with different mechanisms of action have been developed and used during the recent years. Sertraline, citalopram, fluoxetine, escitalopram, paroxetine, and fluvoxamine are among the most widely used antidepressants in young adults and children. Nevertheless, most of these drugs bear the Food and Drug Administration (FDA) black box warning that people under the age of 25 are at high risk of suicidal thoughts (Kadison, 2005; Korczak, 2013).

Determining the depression prevalence, risk factors, identifying and addressing the causes of depression among university students are all a significant part in increasing the academic performance of the students and improving their general health conditions by avoiding chronic disease aggravating factors, prevent the recurrence of them which will lead to decrease the suicide likelihood as well (Hür et al., 2014; İskender et al., 2018). This study therefore aimed to assess the prevalence of depression among university students and identifying their characteristics.

2. Materials and Methods

2.1. Study Design

'Beck Depression Inventory' and demographic properties self-reported scale were used in the study. The study was initiated after the ethical committee approval. Surveys were conducted through online via Google forms. The questionnaire was delivered to all the universities in Istanbul via e-mail and phone by university representatives or research assistants. The questionnaire was sent to the students studying in 27 different departments; and was based on volunteering. 286 students were randomly selected. It took

about 8 minutes to complete the questionnaire. Also, a consent form was received from the students that the information they provided in the questionnaire would be used. The sample size was calculated using the level of the confidence interval of 95% and power at 80%.

2.2. Study Population

University students in Istanbul aged between 18 to 30, who accepted and signed the consent forms included in the study.

2.3. Demographic Variables

Demographic variables such as age, gender, school, department, educational status, antidepressant use, drug name, duration of antidepressant use, lifestyle, social history were documented using a pre-prepared form.

2.4. Beck Depression Inventory (BDI)

This is a self-report scale containing 21 items developed by Beck, Mendelson, Mock, Erbaugh, and Ward to evaluate the severity of the individual's depression (Beck et al., 1961). The questionnaire employed in the study is the Turkish version which has been translated and validated by Hisli (1988).

The students were asked to mark the option that best describes their feelings during the last week. At the end of the survey, the depression levels were classified as following:

- severe depression "30-63 points",
- moderate depression "17-29 points",
- mild depression "10-16 points",
- and lastly the minimal depression was between "0-9 points".

Within the scope of the questionnaire, depressed mood, social withdrawal, feeling of failure, pessimism, weight loss, dissatisfaction, feelings of guilt, crying spells, work inhibition, anxiety, indecision, distortion of the bodily image, sleep disturbance, fatigue, decreased appetite, and loss of libido were assessed (Hisli, 1989). The reliability coefficient of BDI was found to be $\alpha = 0.86$ and where the validity coefficient was $\alpha = 0.75$ (Akçagöz, 2017).

2.5. Statistical Analysis

For all statistical analysis, Statistical Package for the Social Sciences (SPSS) 26 was used. The 95% confidence interval with $p < 0.05$ was used to assess results. As the data is normally distributed means and standard deviations were used to describe participant characteristics. Chisquare cross tabs and independent t-test were executed to determine if significant differences were present among the categorical variables and continuous variables, respectively.

3. Results

3.1 Demographic Characteristics of the Students

The conducted cross-sectional study obtained data from different schools located in Istanbul. The highest participation in the study was from Altınbaş (21.33%), Istanbul (20.63%), Yeni Yüzyıl (10.49%), and Istinye Universities (12.59%). Yeditepe (0.70%), Maltepe (%0.70), Biruni (8.74%), Istanbul Technical (3.85%), Yıldız Technical (5.24%) Istanbul Kültür (1.40%), Bezmialem (5.25%), Beykent (1.75%) and Marmara (7.34%) Universities are other universities that students attended. The study extended over 4 months upon the approval of the ethics committee. The sociodemographic characteristics of the students are shown in Table 1.

A total of 286 out of 600 students consented and completed the study, with a response rate of 47.6%. Also, a total of 286 students who were compatible with the inclusion criteria were asked to complete the questionnaire. The data from the students were collected from 27 different departments most of whom were from the faculty of pharmacy (n=220, 76.92%). The mean age and SD of the student was 21.79 ± 1.775 years, and 75% of the participants were female students. In this study, alcohol use was common among the students (44%), furthermore 27% of them were smokers (Table 1).

Table 1. Demographic and clinical characteristic of the students participating in the study

		n=286
Age (mean ± SD)		21.79 ± 1.775
University types	Private	63%
	Public	37%
Departments	Health sciences	81%
	Physical sciences	14%
	Social sciences	5%
University degree	Associate	0.3%
	Bachelor's	95.5%
	Master/PhD	4.2%
Gender	Female	75%
	Male	25%
Alcohol status	Yes	44%
	No	56%
Smoking status	Smoker	27%
	Non-smoker	73%
Doing sport	Yes	39%
	No	61%
Household composition	Alone (home, dormitory)	56%
	With family	44%
Family structure	Married parents	89%
	Divorced parents	7%
	One parent deceased	4%
Beck scores	Minimal	59%
	Mild	20%
	Moderate	16%
	Severe	5%

Nearly, 11% of the participants stated that they were using antidepressants; however, the SSRIs was the most common antidepressant group used by the participants. Among the SSRIs group, the most used drug was fluoxetine with 33.25% while the use of citalopram and sertraline was 19.35%.

Regarding the duration of antidepressant usage, 55% of the students have been using antidepressant drugs for less than 1 year, 39% have been using them for 1 to 3 years, and 6% for more than 3 years. For instance, while 94% of the students stated that they have received advice from the doctor regarding the use of the antidepressant, the last 4% of the students declared that they have got medical counsel from their pharmacists. The demographic variables, characteristics and the use of antidepressants are shown in Table 2.

Table 2. The questions answered by the students about their antidepressant use

		n=286
Age (mean ± SD)		21.79±1.775
University types	Private	63%
	Public	37%
Departments	Health sciences	81%
	Physical sciences	14%
	Social sciences	5%
University degree	Associate	0.3%
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	Mild	20%
	Moderate	16%
	Severe	5%

90% of students using antidepressants also think their treatments are effective. While 50% of the students using antidepressants indicated positive changes, 10% stated that negative changes were observed, and 40% stated that they did not observe any changes (Table 2).

When asked about the side effects observed with antidepressant use, the students using antidepressants reported that 28% of them were feeling sleepy, 18% suffered from severe anxiety, 18% faced confusion, 18% complains about nausea, 9% suffered from emotional disturbance while 9% experienced movement disorder. Additionally, when the participants were asked if they are planning to stop using their antidepressant drugs, 68% of the students answered "Yes" while the rest 33% answered "No". All the students involved in this study $n=286$ were asked whether they think they need to use antidepressant medicine; 30% of the whole involved population replied: "Yes"; and 70% replied, "No" (Table 2).

Moreover, when the students were asked about the medications other than the antidepressants they used, levothyroxine (25%) and isotretinoin (25%) were found to be the most used drugs.

3.2 Beck Depression Inventory

Demographic variables such as age and gender were recorded, and the Beck score was additionally documented. The mean Beck Score and SD was found to be 13.16 ± 8.17 . Looking at the scores of 286 students noticed that 59% of them suffer from no or minimal depression, 20% mild, 16% moderate, and 5% of them were suffering from severe depression.

3.3 Statistical Analysis Between Demographic Variables and Depression Level

In terms of the significance between the type of university "private or public" and the depression's level ($p < 0.05$), 63% of the participants were studying in a private university while 37% were studying in a public university. The rate of severe depression was 1.9% and 4.9% in students studying at public and private universities respectively (Table 3). For instance, the departments were examined and there was a significant difference between the departments and the levels of depression as well ($p < 0.05$) (Table 3). However, there was no significant difference between the education level "Associate degree, Bachelor's degree, Master/PhD degree" against the level of depression ($p > 0.05$).

Table 3 shows the significant difference between student factors and their level of depression, taking into consideration that severe depression was more common in female participants.

Table 3. The total effect of the students' factors (gender, university type and departments) against the depression level

Factors	No or Minimal Depression	Mild Depression	Moderate Depression	Severe Depression	p* Value
<i>Gender</i>					
Female	53.0%	21.9%	18.6%	6.5%	0.001*
Male	77.5%	15.5%	7.0%	0.0%	
<i>Type of University</i>					
Public	52.3%	26.2%	19.6%	1.9%	0.028*
Private	59.1%	20.3%	15.7%	4.9%	
<i>Departments</i>					
Health science	62.8%	16.5%	15.6%	5.2%	0.023*
Physical science	46.2%	30.8%	17.9%	5.1%	
Social science	37.5%	50%	12.5%	0%	

* p value significant at < 0.05

* p value is given for depression level

With regards to the reasons that the students used the antidepressants, 29% of the students used antidepressants to treat depression while 19% of the students used it only to treat anxiety where no relationship was observed between the depression level and the reason for using the antidepressant drugs. Furthermore, some students stated that they have used antidepressants for the treatment of diseases such as obsessive-compulsive disorder, panic attack, and post-traumatic disorder. For instance, there was a significant difference between the need for antidepressant medications and the level of depression ($p=0.001$). Where severe depression was observed in 11.7% of the students who stated that they needed antidepressant medication, the rest 73% of those who did not need antidepressant medications showed minimal depression in Beck score (Table 4).

Table 4. The ratio of the students' antidepressants needs and their level of depression

Do you think you need an antidepressant?	Minimal Depression	Mild Depression	Moderate Depression	Severe Depression	p* value
Yes	29.9%	28.6%	29.9%	11.7%	0.001*
No	73.6%	18.0%	6.7%	1.7%	

* p value significant at < 0.05

* p value is given for depression level

In terms of the significance between the family structure and the level of depression ($p<0.05$), severe depression was more common in students with divorced parents (21.1%), orphan students (16.7%), and students with married parents (3.1%), respectively (Table 5).

Table 5. The total effect of the family structure on the depression level of the students

Family status	Minimal Depression	Mild Depression	Moderate Depression	Severe Depression	p* value
Married parents	59.6%	20.8%	16.5%	3.1%	0.012*
Divorced parents	52.6%	15.8%	10.5%	21.1%	
One parent deceased	58.3%	16.7%	8.3%	16.7%	

* p value significant at < 0.05

* p value is given for depression level

However, no significant correlation was found between alcohol use or smoking and level of depression ($p > 0.05$). It was observed that there were no significant differences between the level of depression and other medications such as levothyroxine or isotretinoin used ($p > 0.05$). Besides, there was no significant difference between age and depression level ($p > 0.05$). Also, there was no significant difference between the education level “Associate degree, Bachelor’s degree, Master/PhD degree” against the level of depression ($p > 0.05$).

4. Discussion

From a psychological point of view, any changes in lifestyle, either good or bad, may lead to stress and anxiety. Starting the university is one of the major changes in life for the students as they have to make their own decisions, develop the ability to act independently and individually. These changes are accompanied by emotional changes, depression, and anxiety which may affect their academic performance and quality of life (Hür et al., 2014).

This study was conducted to determine the level of depression in university students and the risk factors affecting this condition. Demographic variables such as age and gender were recorded and the Beck score was additionally documented.

In a study conducted in Iran, the depression prevalence of university students was found to be 33% (Sarokhani et al., 2013). However, they did not find any significant difference between the genders as in our study. Also, a total of 113 studies were included in a study from China to estimate the depression prevalence among college students. It has been observed that the prevalence of depression in China is 28.4%. In another study conducted with 631 university students in the United States, it was stated that 46.94% of the participants showed mild to severe depression symptoms. Similar to our study, higher depressive symptoms were observed in women compared to men. In a study conducted in Tanzania with 1047 participants, 21.7% of the students had moderate to severe depression. In our study however, the prevalence of depression from mild to severe symptoms was observed to be 40.9%. This result is very similar to the study done in the United States. Generally, differences may have been caused by

different measurement tools, different methods, or cultural differences (Acharya et al., 2018; Gao et al., 2020; Lugata et al., 2020)

According to the literature, females suffer from depression in higher rates comparing to males especially during their adolescencehood (Kessler & Walters, 1998). In our study, there was a significant difference between the students' gender and their level of depression ($p < 0.05$); for instance, the female students were more prone to depression than the male students.

A study conducted by Mirowsky & Ross (1992) has shown that the depression occurrence rate is the highest among elderly people, a little bit lower among the young and adults where the lowest depression rate was seen among the middle-aged people. In this study conducted with university students who are considered as young adults as their mean age was 21.79 ± 1.775 years, no significant relationship was found between the age of the students and their depression level (23 years \geq 86%, 23 years $<$ 14%). This may be due to the narrow age range of the participants (18-30 years old).

In a study conducted by Adewuya et al. (2006) with university students in Western Nigeria, a strong correlation was found between smoker or alcohol users and their level of depression. However, in this study, smoking or alcohol use did not affect the level of depression, which suggests the necessity of detailed research focusing on smoking and alcohol addiction among university students.

Another trial conducted by North et al. (1990) regarding the effect of physical exercises on depression level, reported that the depression rate was less in the group who are physically active. However, in this study, there was no significant difference between the physically active and inactive students regarding their depression level ($p > 0.05$).

Although the brain produces endorphins during the exercises which have a positive effect on depression, this study did not support this statement. The reason may be that students' depression levels were not observed before and after the exercises in addition to the small sample size. That is why the subsequent studies may record the depressive symptoms experienced by participants before and after exercise to observe the effect of physical activity on depression more clearly (North et al., 1990).

In this study, a significant difference was observed between the university type and the depression level, higher depression rates have been seen in students who are studying in private universities than those who are studying in public ones. The reason should be investigated to understand if the students are suffering from financial problems that lead to be depressed or suffering from facing issues related to the education environment. As a result of a study conducted among medical faculty students in Pakistan with 300 participants, it was stated that more depression was observed in public universities compared to private universities (Zafar et al., 2017). In a study conducted in Jordan with 455 student participants, it was stated that the mental health level of students studying at private universities was higher than those studying at a state university (Alhabees et al., 2018).

In this study, 81% of the involved students were from health science faculties where 14% of them were from faculty of physics and the last 5% were studying social sciences. A significant relationship was found between the departments and the students' depression level ($p < 0.05$). Severe depression was higher

among students studying in the health science faculties (5.2%) and physical sciences (5.1%) compared to students studying in the faculty of social sciences (0%). Mild depression was observed with a rate of 50% among students studying in social sciences. Possible reasons such as difficult lessons and a higher number of exams may be faced in students who showed depressive symptoms.

According to the results of our study, 11% of the students who participated were using antidepressant drugs and the SSRIs were the most used drug with the favor of 77%. Maruf et al. (2019) stated that the most used antidepressant class in young adults and children are SSRIs. Although their clinical effectiveness is similar to that of the tricyclic antidepressants (TCAs), they are better tolerated and safer as the overdoses are less toxic than the others. Moreover, SSRIs have a lot of clinical properties for a better choice as the low incidence of weight gain, less anticholinergic effects, alleviating sleep disturbance in depression without causing psychomotor dysfunction during the day, and they have a role in managing depression-related anxiety (Lane et al., 1995). However, it should be noted that SSRIs have some side effects and patients should be informed about all the treatment options and their uses, advantages, and side effects.

The duration of antidepressant usage varies between students. 55% of the students have been using antidepressant drugs for less than 1 year, 39% have been using them for 1 to 3 years, and 6% for more than 3 years. The treatment of depression consists of three phases:

Acute phase where the remission is induced (minimum 6 – 12 weeks in duration). The purpose of this phase is to stabilize the first depressive symptoms, cooperate with the patient, providing training, selecting the best fit treatment, and assessing the response. The second one is the continuation phase where the remission is preserved, and relapse is prevented (6 months or more after remission). The purpose of this period is to prevent the exacerbation or recurrence of a current attack, while in the maintenance phase – susceptible patients are free for relapses (12 to 36 months in duration). Patients with significant risk factors should undergo maintenance treatment in maximum doses (Cohen, 1997; Demyttenaere, 2001). This means that most of the students stop their medication directly after the induction phase which may indicate the necessity of follow up with these students to evaluate the possibility of relapse symptoms.

Patients who have a complex, variable clinical picture of major depressive disorder may need a multimodal treatment including education, psychotherapy, and pharmacotherapy. Clinical responses, including suicidal thoughts, adverse effects, and behaviors should be monitored during the treatment of depression. To promote compliance to the treatment, an awareness session should be done with the patients themselves and their families about the side effects that may be seen during the treatment period (Gelenberg et al., 2010). The average recovery time which may extend to 6 months should be discussed as well besides the probability of getting a new attack in the future (Gelenberg et al., 2010). Pharmacists may play a significant role in the treatment of the patients suffering from depression by:

- giving recommendations, assessing patients' adherence,
- counseling about medicines,
- and following up with the patients regarding the drug side effects (Demyttenaere, 2001).

Patients who do not benefit from treatment or who experience intolerable side effects should be referred to a doctor (Scheerder et al., 2008). Considering the adverse effects, most of the students complained about drowsiness, severe anxiety, confusion, and nausea. These side effects were one of the reasons that forced 68% of the participants to discontinue the medication. To choose the most suitable antidepressant for each patient, his/her medical file should be evaluated individually. The role of the clinical pharmacist could be seen here clearly, as he/she is the only eligible person to make the best treatment option taking the patient preferences and the possible side effects into consideration.

Although a study done by Wysowski et al. (2001) found a relationship between depression, suicide, and isotretinoin, our study did not show any relationship between the level of depression and the other medications used. Sokratous et al. (2014) in their study which involved 1500 university students reported a higher prevalence of depressive symptoms than the students who were living alone. In this study, most of the students were living away from their homes but no significant difference was found ($p > 0.05$). In this study, there was a significant relationship between the pattern of the students' families and their depression level ($p < 0.05$). There is substantial evidence that depressed adults and children experience difficulty in family lives, such as marital discord or disruption (Burbach & Borduin, 1986; Keitner & Miller, 1990). Sokratous et al. (2014) indicated in their study that the incidence of clinical depressive symptoms was higher in orphan students or those who have divorced parents. The study, conducted by Ngin et al. (2018) over 403 university students, has shown the same aspect as well. This also goes in the same line with our study and it can be explained by the fact that parents' divorce can cause a decrease in the family moral and material support which may lead to a depressive disorder or even traumatic stress for the child (Sokratous et al., 2014).

The results of the study should be evaluated considering some limitations that need to be outlined, all the data are subjective affecting the reliability of the study. Some students did not want to state that they used antidepressants. So, although the rate is high, the number of students who used antidepressants may be underestimated. Lastly, the study is limited with only university students in Istanbul.

Conclusion

As a result of the study, it was observed that although depression is not very common among university students, it has a rate that cannot be underestimated. Severe depression has been observed especially in individuals studying at the faculties of health science, physics, and life sciences, students studying at a private university, and those who are experiencing negative family impacts. Additionally, being female is also a risk factor for depression.

Among the students, SSRIs were the most used antidepressant class and since these drugs have serious side effects, individuals should be monitored by healthcare professionals to taper the doses safely. Health education and psychological units of the schools are extremely important for individuals at high risk of developing mental illnesses. Besides, workshops on depression management should be organized for students to teach them how to cope with stress and prevent depression.

Ethical Approval

All procedures performed in this study involving human participants followed the ethical standards of the institutional and/or national research committee (Institutional Review Board of Medipol University 27.11.2019/1006) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

Authors declared no conflict of interest.

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Research Article

The Burden of Care and Coping Strategies of Caregivers of Elderly Patients



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Abstract: This study was conducted to determine the burden of care and coping strategies experienced by caregivers of elderly inpatients in a palliative care unit and internal medicine services. This study is a descriptive and comparative study. The study sample consisted of 80 caregivers of the elderly hospitalized in the Palliative Care Unit and Internal Medicine Clinic in a city hospital between April and June 2017. The Personal Information Form, the Zarit Caregiver Burden Interview Scale (ZCBI Scale), and Coping Strategies Inventory-Short Form (CSI Short Form) were used in this study. The total score obtained by the caregivers from the ZCBI Scale was 50.37 ± 10.93 in the palliative care unit and 32.72 ± 8.72 in the internal medicine clinic. A significant difference was found between the two groups in terms of the subscales "Planning" and "Searching Social Support-Instrumental" of the CSI Short Form and the total score of ZCBI Scale. Nurses should assess socio-demographic characteristics, financial difficulties, and family relationships that may intensify the burden on caregivers of elderly patients in the palliative care units and facilitate coping strategies.

Keywords: *Burden; coping; elderly; nursing; palliative care*

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1. Introduction

A caregiver is someone who has a responsibility to support the patient physically, socially, emotionally, and financially (Veloso, and Tripodoro, 2016). As the burden of care increases, the caregiving-receiving relationship can be transformed into a troublesome, one-way, dependent, intense, and long-term obligation for caregivers. Additionally, the level of burden on caregivers increases when this obligation is inconsistent with the caregivers' other needs and wishes (Aires et al., 2017).

The burden of care is used to express the physical, psychological, social, or economic problems that caregivers may experience while providing care (Liu et al., 2017; Parker et al., 2016). This phenomenon may cause caregivers to experience depression and anxiety, deterioration of health, increased referrals to the doctor, and increased drug use. The nature of the disease whether chronic or terminal as well as the caregivers' close affinity to their patients adds to the burden. Comparatively, the resources allocated for care and the increased psychological and social problems impact the burden of care experienced by caregivers which leads to changes in their social roles (Hsu et al., 2017; Macneil, 2010; Mollica et al., 2017; Schulz, 1999; Terakye, 2011; Weissman, and Meier 2011). As the quality of life of the patient deteriorates with increased symptoms to manage an uncertain prognosis, the quality of life of the caregiver is negatively affected (Walczak et al., 2017).

Coping is the struggle of an individual to prevent or overcome internal and external pressures (Eslami et al., 2016; Vitorino et al., 2018). Coping is also defined as a dynamic process with cognitive and behavioral reactions to reduce psychological distress or stress-causing sources (Bacanli et al., 2013). Caregivers of patients with chronic diseases must constantly adapt to changing conditions, providing care for both patients and themselves. Therefore, they need to maintain various coping behaviors to adapt (Eslami et al., 2016).

According to the World Health Organization (WHO), one of the primary goals of palliative care is to focus on the needs of patients and their caregivers (WHO, 2012). Therefore, healthcare professionals need to determine the needs of caregivers and work toward solutions to the identified needs through planning, implementing, and evaluating appropriate interventions.

Care burden causes more depression and anxiety, and deterioration in health in caregivers and makes them visit their doctor more and use more drugs. In time, the personal care of the patient, like washing and feeding, comes to be perceived as more difficult than meeting the impersonal care needs of the patient (Mollica et al., 2017).

Studies conducted on cancer patients and their caregivers have found that longer care periods increase care burden and depression in caregivers and that care burden is higher among caregivers who provide care for patients with malign tumors and more symptoms of the disease (Orak and Sezgin, 2015; Yildirim et al., 2013). It was also found that 80.3% of caregivers perceive their health to be good before providing care while 51.6% perceive their health to be bad after they have started to provide care (Orak and Sezgin, 2015). In another study, it was found that caregivers in worse economic situations have a greater care burden (Kalinkara and Kalayci, 2017).

The caregivers of patients with chronic diseases must constantly adapt to a variety of conditions providing care for patients and themselves and exhibit various coping behaviors to manage this situation (Eslami et al., 2016).

Nurses should assess the level of burden experienced by families, especially those who care for elderly patients in the palliative care unit. Additionally, relevant coping strategies should be developed. Elderly patients can receive better support in long-term care and more successful outcomes with activities of daily

living by reducing the level of burden on caregivers and facilitating relevant coping strategies. Therefore, it is important to determine the care burden of elderly patients on caregivers.

1.1. Aim

This study was conducted to determine the burden of care and coping strategies experienced by caregivers of elderly inpatients in a palliative care unit and internal medicine clinic.

2. Materials and Methods

2.1. Study design

This descriptive and comparative study was carried out between April and June 2017 in the Palliative Care Unit and Internal Medicine Clinic of Kahramanmaraş Necip Fazıl City Hospital.

2.2. Study participants

The definition and classifications of old age are mostly concerned with the physiological and chronological dimensions of old age. According to WHO and ONS (Office for National Statistics), big majorities of countries have chosen an optional chronological age of 60 or 65 as a definition of 'older person' (BMA, 2016; WHO, 2018). The participants in the present study were family caregivers of 80 patients over 65 years old who were hospitalised at the Palliative Care Unit and Internal Medicine Clinic of Kahramanmaraş Necip Fazıl City Hospital during the data collection period. The inclusion criterion was being the person (over the age of 18) who spends the most time caring for the patient with over 65 years old, i.e., the main caregiver. Caregivers were eligible if they provided for the last one months or more and were looking after a care-recipient with at least one chronic medical condition. The pilot study was conducted with the inclusion criteria for the appropriate 6 caregivers. Caregivers participating in the pilot study were not included in the study. The study sample was determined by performing a power analysis in the G*power statistical program. Significance level (α), statistical power ($1 - \beta$), and effect size were determined as 0.05, 0.80, and 0.74, respectively, in previous studies which often used an experimental group of 30 caregivers giving palliative care and a control group of 30 caregivers giving non-palliative care (Bacanlı et al., 2013). The study sample consisted of a total of 80 caregivers who agreed to participate in the study, including 40 caregivers from the palliative care unit and 40 caregivers from the internal medicine clinic. The power of this study was calculated using T test, effect size 0.96 (high size), significance level 0.05 and statistical power $(1 - \beta) = 0.95$.

2.3. Data Collection

Data collection was carried out in the Palliative Care Unit and Internal Medicine Clinic. The data were collected by face-to-face interview method. A researcher approached caregivers who were initially identified as main caregivers of patients by clinical nurses. The researcher explained the purpose of the

study, checked eligibility, and invited main caregivers to participate in the study. A personal information form prepared by the researcher, the Zarit Caregiver Burden Interview (ZCBI), and Coping Strategies Inventory-Short Form (CSI Short Form) were used during the caregiver interviews. Each caregiver was interviewed for 35-40 minutes. Tools used to assess caregivers are as follows:

2.4. Measures

2.4.1. Personal Information Form

Researchers examined literature and prepared this form to determine the sociodemographic characteristics of the caregivers included in the study. In addition to the sociodemographic characteristics of caregivers in the personal information form, there are questions such as the length of care that caregivers allocate to the individual, how caregivers look after the patient, how difficult caregivers are having to care, and how caregivers cope with these difficulties (Ateş and Bilgili, 2013; Tarı Selçuk, and Avcı 2016).

2.4.2. Zarit Caregiver Burden Interview (ZCBI)

Zarit, Reever, and Bach-Peterson developed the scale in 1980. It measures the stress experienced by caregivers. It consists of 22 questions aimed at determining the effect of caregiving on an individuals' life. The questions can be self-reported or through interview techniques. The scale has a Likert-type score ranging from 1 to 5 (1=never, 2=rarely, 3= sometimes, 4=often and 5=always). A high score indicates a higher frequency of experiencing stress. The validity and reliability study for the Turkish population was carried out by Ozlu et al., (2013). Cronbach's alpha value of the scale was found to be 0.92 in this study (Kaiser-Meyer-Olkin (KMO) = 0.871, $\chi^2 = 1119.785$, $p=0.000$).

2.4.3. Coping Strategies Inventory-Short Form (CSI Short form)

Carver (1997) developed an instrument with fewer questions, taken from the long-form of the Coping Strategies Inventory. This short version is composed of 14 factors, each with two items. As in the long-form, each subscale is evaluated separately. Low scores indicate that the subscale is used less, and high scores indicate that the subscale is used more.

The validity and reliability study for the Turkish population was carried out by Bacanlı et al., (2013). For this study, Cronbach's alpha value of the scale was found to be 0.66 (Kaiser-Meyer-Olkin (KMO) = 0.540, $\chi^2 = 720.181$, $p = 0.000$).

2.5. Analysis

IBM SPSS Statistics 22 statistical program was used to analyze the data. Percentage values, arithmetic mean, standard deviation, minimum and maximum values were given as descriptive statistics of the data. The Shapiro-Wilk normality test was used to determine whether the data showed a normal distribution. Data were found to show a normal distribution. Data were evaluated using t-test, chi-square analysis,

and Pearson's correlation in independent groups. The significance level p value of <0.05 is considered as significant.

2.6. Ethical Consideration

The study was approved by an ethics committee (ID: 2017/111). All participants provided verbal and written informed consent. Written informed consent has been obtained from patients and the patient's family/guardian for publication of the data. The participant was verbally informed by the researchers with the following information; why is he/she included in the study, how many minutes the survey will last, his/her responses to this survey will be kept confidential and anonymous, he/she *can leave this research study at any time*. Permission for the study was obtained from the institution involved in the study.

2.7. Limitation of The Study

The sample size of this study is relatively small, which may limit the study's generalizability. However, samples of this and smaller sizes have been found adequate in some studies (Hagell et al., 2017). Nonetheless, assessments based on larger samples are warranted to allow for strong results, especially regarding dimensionality and functioning.

3. Results

Table 1 shows the sociodemographic characteristics of the caregivers of elderly patients. The participants: 65% of them were female, the majority were over 36 years old and 80% were married. Further, 81.3% were unemployed, 38.8% were primary school graduates, 70% had health insurance and 55% did not suffer from chronic diseases. Most of the caregivers were daughters or spouses of the patients (Table 1).

Table 1. Sociodemographic characteristics of caregivers of older inpatients hospitalized in PCU and IMC (n=80).

		PCU		IMC		Total		Test*
		n	%	n	%	n	%	
Gender	Female	24	60.0	28	70.0	52	65	p= 0.482
	Male	16	40.0	12	30.0	28	35	
Age	18-25	7	17.5	2	5.0	9	11.3	p=0.360
	26-35	5	12.5	6	15.0	11	13.8	
	36-50	13	32.5	16	40.0	29	36.3	
	Above 50	15	37.5	16	40.0	31	38.8	
Marital status	Married	29	72.5	35	87.5	64	80	p=0.243
	Single	7	17.5	3	7.5	10	12.5	
	Divorced/widowed	4	10.0	2	5.0	6	7.5	
Children	Yes	29	72.5	33	82.5	62	77.5	p=0.422
	No	11	27.5	7	17.5	18	22.5	
Employment Status	Employed	8	20.0	7	17.5	15	18.8	p=0.775
	Unemployed	32	80.0	33	82.5	65	81.3	
Educational Status	Illiterate	11	27.5	14	35.0	25	31.3	p=0.064
	Primary education	12	30.0	19	47.5	31	38.8	
	High school	8	20.0	6	15.0	14	17.5	
	Associate Degree	4	10.0	0	0	4	5	
Undergraduate	5	12.5	1	2.5	6	7.5	p=0.795	
	Poor	4	10.0	6	15.0	10		12.5
	Middle	21	52.5	20	50.5	41		51.3
Good	15	37.5	14	35.5	29	36.3	p=0.626	
	Health Insurance	Yes	29	72.5	27	67.5		56
No	11	27.5	13	32.5	24	30	p= 1.00	
	Chronic Disease	Yes	18	45.0	18	45.0		36
No	22	55.0	22	55.0	44	55	p=0.479	
	Patient Relationship	Caregiver	1	2.5	1	1.3		2
Mother		0	0	2	2.5	2		2.5
Father		0	0	1	1.3	1		1.3
Sibling		2	5	1	1.3	3		3.8
Spouse		7	17.5	11	13.8	18		22.5
Daughter		11	27.5	13	16.3	24		30
Son		10	25	6	7.5	16		20
Other		9	22.5	5	6.3	14	17.5	

*Crosstabs analysis, PCU: Palliative Care Unit IMC: Internal Medicine Clinic

Table 2 illustrates the aspects of providing care to elderly inpatients in the PCU and IMC. There was a significant difference between these two groups in terms of the time allocated to patient care, the most difficult situation in providing care for patients, and the coping strategies for difficulties in providing patient care. Of the caregivers, 55% allocated 13 hours or more per day to patient care, 35% had the most difficulty providing personal care for their patients and 37.5% of them coped with difficulties in

carers by receiving support from other family members in the PCU. Also, 32.5% of them felt the need for psychosocial support. Conversely, in the other group of these caregivers, 20% coped with difficulties by receiving support from other family members. This other group includes the patient's brother, son's wife, and friend. Besides, 15% of them felt the need for psychosocial support, 20% coped by being patient and 17.5% used other methods in the IMC, 12% used other methods (respectively, praying and receiving spiritual support) in the PCU. However, 15% did not find a solution for their problems (Table 2).

Table 2. Comparison of caregivers' characteristics of caregivers (n=80)

		PCU		IMC		Total		Test*
		n	%	n	%	n	%	
Time Allocated for Patient Care	Takes no time	0	0	16	40.0	16	20.0	X ² =45.329 p=0.001
	0-3 hours	1	2.5	11	27.5	12	15.0	
	3-6 hours	3	7.5	6	15.0	9	11.3	
	7-12 hours	14	35.0	4	10.0	18	22.5	
	13 hours and above	22	55.0	3	7.5	25	31.3	
Time Spent for Patient Care	1-3 months	9	22.5	12	30.0	21	26.3	X ² =8.992 p=0.109
	3-12 months	13	32.5	5	12.5	18	22.5	
	1-2 years	3	7.5	2	5.0	5	6.3	
	2-3 years	3	7.5	3	7.5	6	7.5	
	3-4 years	5	12.5	2	5.0	7	8.8	
The Most Challenging Situation in Patient Care	More than 4 years	7	17.5	16	40.0	23	28.8	X ² =35.382 p=0.001
	Patient's personal care	14	35.0	6	15.0	20	25.0	
	Patient's insufficient oral intake	7	17.5	0	0	7	8.8	
	Patient's unconscious behaviors	5	12.5	1	2.5	6	7.5	
	Patient's infectious diseases	1	2.5	2	5.0	3	3.8	
	Caregiver's inadequate time	3	7.5	0	0	3	3.8	
	Patient's violation of dietary rules	0	0	8	20.0	8	10.0	
	Other	10	25.0	12	30.0	22	27.5	
None	0	0	11	27.5	11	13.8		
Coping Strategies for Challenges of Patient Care	Hiring a caregiver for patient care	3	7.5	0	0	3	3.8	X ² =28.908 p=0.001
	Receiving support from family members	15	37.5	8	20.0	23	28.8	
	Getting home-care pay	2	5.0	0	0	2	2.5	
	Applying to hospital	10	25.0	6	15.0	16	20.0	
	Getting assistance from home-care services	4	10.0	0	0	4	5.0	
	Being patient	1	2.5	8	20.0	11	13.8	
	Other	5	12.5	7	17.5	9	11.3	
	None	0	0	11	27.5	12	15.0	
Living with the patient	No	18	45.0	17	42.5	35	43.8	X ² =0.051
	Yes	22	55.0	23	57.5	45	56.3	p=0.822
Psychosocial Support Request Status	Yes	13	32.5	6	15.0	19	23.8	X ² =3.382
	No	27	67.5	34	85.0	61	76.3	p=0.066

*Chi Square Test, PCU: Palliative Care Unit, IMC: Internal Medicine Clinic

The caregivers in both settings received the highest coping score on the subscale of “mental disengagement”. The mean score from the CSI Short Form subscale of “planning” in the PCU was found to be 3.57 ± 1.41 and 4.45 ± 1.01 in the IMC. The mean score from the CSI Short Form subscale of “use of instrumental social support” in the PCU was found to be 6.32 ± 0.99 and the mean score in the IMC was found to be 5.67 ± 1.20 . The mean total score from the ZCBI was found to be 50.37 ± 10.93 in the PCU and 32.72 ± 8.72 in the IMC (Table 3).

Table 3. Comparison of the groups’ scores on Coping Strategies Interview Short Form Subscales and Zarit Caregiver Burden Interview

	Group	X ± SD	t	p
CSI Short Form Subscales				
Active coping	IMC	6.07 ± 1.02	1.359	0.178
	PCU	6.35 ± 0.76		
Planning	IMC	4.45 ± 1.01	-3.186	0.002
	PCU	3.57 ± 1.41		
Use of instrumental social support	IMC	5.67 ± 1.20	2.626	0.001
	PCU	6.32 ± 0.99		
Use of emotional social support	IMC	2.37 ± 0.70	- 0.646	0.520
	PCU	2.27 ± 0.67		
Focus on & Venting of emotions	IMC	5.97 ± 1.02	1.053	0.296
	PCU	6.25 ± 1.29		
Behavioral disengagement	IMC	4.87 ± 0.85	1.484	0.142
	PCU	5.20 ± 1.09		
Mental disengagement	IMC	6.67 ± 0.97	0.660	0.511
	PCU	6.82 ± 1.05		
Positive Reinterpretation & growth	IMC	4.52 ± 1.35	-1.868	0.066
	PCU	3.95 ± 1.39		
Denial	IMC	4.80 ± 0.93	- 0.815	0.418
	PCU	4.60 ± 1.21		
Acceptance	IMC	5.07 ± 1.16	0.772	0.443
	PCU	5.27 ± 1.15		
Religious Coping	IMC	5.75 ± 0.95	-1.193	0.236
	PCU	5.52 ± 0.71		
Substance Use	IMC	5.12 ± 0.99	-0.606	0.546
	PCU	5.00 ± 0.84		
Humor	IMC	5.50 ± 1.19	1.695	0.094
	PCU	5.95 ± 1.17		
Self-blame	IMC	5.22 ± 0.89	0.648	0.519
	PCU	5.35 ± 0.83		
Total Score of ZCBI	IMC	32.72 ± 8.72	7.979	.001
	PCU	50.37 ± 10.93		

*Student t test, PCU: Palliative Care Unit IMC: Internal Medicine Clinic, ZCBI: Zarit Caregiver Burden Interview, CSI: Coping Strategies Interview

A weak and positive relationship was found between the scores of the CSI Short Form subscale of “active coping” and the ZCBI ($p < 0.05$) for the caregivers in the PCU. Besides, a weak and negative relationship was found between the scores of the CSI Short Form subscale of “planning” and the ZCBI, whereas a weak and positive relationship was found between their scores from the CSI Short Form subscale of “self-blaming” and the ZCBI in the PCU ($p < 0.05$). On the other hand, for the caregivers of elderly inpatients in the IMC; a weak and positive relationship was found between the scores from the CSI Short Form subscale of “self-blaming” and the ZCBI ($p < 0.05$) (Table 4).

Table 4. The relationship between scores on CSI Short Form Subscales and ZCBI received by caregivers of older inpatients in PCU and IMC (n=80)

CSI-SF Scale Subscales	Total Score of ZCBI					
	PCU			IMC		
	r	p	N	r	p	N
Active coping	0.350	0.027	40	-0.225	0.163	40
Planning	-0.340	0.032	40	-0.160	0.324	40
Use of instrumental social support	-0.019	0.910	40	-0.009	0.957	40
Use of emotional social support	0.017	0.918	40	-0.004	0.982	40
Focus on & Venting of emotions	0.024	0.883	40	-0.009	0.954	40
Behavioral disengagement	-0.024	0.885	40	0.220	0.843	40
Mental disengagement	-0.080	0.621	40	0.186	0.251	40
Positive Reinterpretation & growth	-0.242	0.132	40	-0.032	0.172	40
Denial	-0.044	0.789	40	-0.007	0.966	40
Acceptance	-0.169	0.298	40	-0.026	0.875	40
Religious Coping	-0.311	0.051	40	-0.101	0.517	40
Substance Use	0.050	0.760	40	-0.381	0.537	40
Humor	0.287	0.073	40	-0.06	0.713	40
Self-blame	0.320	0.044	40	0.106	0.015	40

*Pearson Correlation Analysis, PCU: Palliative Care Unit IMC: Internal Medicine Clinic, ZCBI: Zarit Caregiver Burden Interview, CSI: Coping Strategies Interview

4. Discussion

The caregiving process is distressing in terms of both caregivers and patients. Chronic and terminal illnesses involve a high level of care due to the severity of symptoms and the resources needed for the patient. The close affinity to their patients, the amount of time and money they spend for patient care, and the increase in psychological and social problems experienced by caregivers increase their burden of care and lead to changes in their social life (Mollica et al., 2017). Health professionals need to support caregivers, plan multidimensional initiatives, manage the implementation and assess outcomes. Caregivers face a multitude of tasks such as monitoring and controlling patient symptoms and ensuring patients receive medical treatments. Also, problem-solving and decision-making, providing emotional support,

and coordinating patient care are tasks for caregivers. Tasks also include ensuring patient safety and providing an environment of care and appropriate equipment (Polat, 2011).

In this study, as in other studies, most of the caregivers were women, which is an expected result due to the cultural characteristics of Turkey (Küçükgüçlü et al., 2009; Pérez-Cruz et al., 2017; Tarı Selçuk and Avcı, 2016; Uzelli Yılmaz and Sarı, 2017). Additionally, the task of caregiving is often left to more experienced and unemployed individuals. Working conditions and ages of the caregivers in this study are similar to those in the literature (Küçükgüçlü et al., 2009; Pérez-Cruz et al., 2017; Tarı Selçuk and Avcı, 2016). Most of the caregivers in this study were the daughters of the patient, and more than half of the caregivers lived in the same house with the patient. Like this study, other studies have reported that the task of caregiving is mostly left to the daughter of the person receiving care (Ateş and Bilgili 2013; Küçükgüçlü et al., 2009; Perez-Ordóñez et al., 2016).

While 55% of the caregivers of elderly patients receiving palliative care spend 13 hours or more a day on patient care, the majority care for patients between 0 and 1 year. Conversely, most of the caregivers (40%) in the IMC reported they have not monitored times for patient care. All the results obtained showed 31.3% of the caregivers provided patient care for 13 hours or more per day, and most of them provided care for more than 4 years. The caregivers of inpatients in the PCU and IMC provided more daily care (in hours) and have longer periods of care than in other units examined in other studies (Ateş and Bilgili 2013; Naef et al., 2017; Tarı Selçuk and Avcı 2016). Considering the cultural structure in Turkey, the notion of family is very important among the people in the Eastern and Southeastern regions. Therefore, the care given to the elderly is mostly provided by the family of the elderly individual, not in private or state care institutions (Ateş and Bilgili 2013; Tarı Selçuk and Avcı 2016).

This study found that the care burden scores of the caregivers with palliative care patients were higher than those giving care to patients in the internal medicine clinic. The review of other studies showed the care burden of the patient group requiring high-intensity care was heavier than those who required low-intensity care (Naef et al., 2017; Spatuzzi et al., 2017; Tarı Selçuk and Avcı, 2016; Vahidi et al., 2016). This shows that the current study complies with the studies in the literature.

There are no studies on coping strategies for the burden of care, but studies of similar subjects were evaluated. Ateş and Bilgili (2013) stated caregivers' coping strategies for stress vary according to the degree of their patients' dependency levels. This study found that coping strategies of the caregivers of elderly inpatients in the PCU differed from those of the caregivers in the IMC. As the burden of care on the caregivers in the PCU increased, their ability to plan decreased, and self-blame increases. Perez-Ordóñez et al. (2016) found a positive relationship between anxiety with the perceived burden of care and non-functional coping, whereas a negative relationship between anxiety and emotional-focused coping was determined. Richardson et al. (2016) found that post-traumatic stress disorder was high and positively correlated with the coping subscales of behavioral disengagement, refusal, and humor.

Conclusion

Caregivers of elderly inpatients in the PCU were found to suffer from a higher burden of care than those in the IMC. In terms of coping strategies, the caregivers of elderly inpatients in the IMC received higher scores in the “planning” subscale, and the caregivers in the PCU received higher scores in the “use of instrumental social support” subscale. Recommendations based on the study are; nurses in the PCUs be increasingly supportive of caregivers especially those of elderly patients and pay close attention to their distress and problems. Nurses should routinely assess the burden of care levels on caregivers and implement plans to address the problem. Caring for caregivers of elderly patients by providing supportive nursing intervention to provide physical, emotional, social, and financial support to decrease their burden and develop coping strategies must be considered for caregiver support. Detailed information about terms of “burden of care” and “coping”, the burden of care assessment tools should be provided in-service training. Strategies for coping should be explained in discharge training to the patient and the caregiver. Further studies are recommended to improve various coping strategies for reducing the burden of care on caregivers of patients in palliative care.

Ethical Consideration

The study was approved by the Gaziantep University Ethics Committee for Non-Interventional Clinical Investigations (2017/111) and all participants gave verbal approval.

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Exhibitor Consent

Informed consent has been obtained from or patient’s family/guardian for publication of the case report and accompanying images. Permission for the study was obtained from the institution involved in the study.

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Conflict of Interest

Authors declare no conflict of interest.

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A New Approach in Epilepsy Treatment: Nano-Carrier Systems

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Abstract: Central nervous system (CNS) diseases have a very important place in terms of public health. Epilepsy is one of the most common CNS diseases. Epilepsy is a chronic disease, and it is a cause of substantial morbidity and mortality. Many people around the world suffer from epilepsy, and the causes of this disease are still not fully clarified. It is known that approximately 50 million people suffer from epilepsy. Antiepileptic drugs are frequently used in the treatment of epilepsy, but the difficulty with these drugs is the emergence of drug resistance, and additionally, antiepileptic drugs can be administered in oral and intravenous routes. But these treatments are not always effective. On the other hand, drugs used in the treatment of epilepsy must be delivered effectively and safely, so to protect the brain. Therefore, new delivery systems are needed to deliver drugs at concentrations determined for high therapeutic efficacy in epilepsy without side effects. Considering this information, there is a need to develop new treatment strategies. With the development of nanotechnology, it has been shown that nanoparticles as a drug delivery system are significantly effective in the treatment of diseases. Nano-carrier systems can fulfill many functions such that they can cross the blood-brain barrier (BBB) passing a specific cell or signaling pathway, reply to endogenous stimulus, support nerve regeneration, and ensure cell survival. Thanks to these features, it is seen that nano-carrier systems are quite assertive regarding the current treatment methods in epilepsy. Today, studies of the therapeutic efficacy of liposomes, micelles, solid lipid nanoparticles, dendrimers, and nanoemulsions as nano-carrier systems on central nervous system diseases are still ongoing. It holds promise in the concentration control of the drugs and the delivery of the drug to the target tissue through the BBB. This review investigates the role of nano-carrier systems in addition to current treatment methods in epilepsy.

Keywords: *Epilepsy; epidemiology; nano-carrier systems; nanotechnology*

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1. Introduction

Epilepsy is a neurological disease characterized by abnormal electrical activity that causes seizures in different parts of the brain. This disease has neurological, cognitive, psychological, and social effects; and globally influences roughly 50 million people (Devinsky et al., 2018). Estimates of the global prevalence and incidence of epilepsy vary from country to country. While it is more common in middle-income countries than in high-income countries, there is a significant increase in the number of patients in childhood compared to old age (Fiest et al., 2017). However, the mortality is low. It was seen that unintentional injuries and suicide were among the deaths caused by epilepsy (Thurman et al., 2017). These results show that the patients are psychologically affected by life-long continuation of the disease.

According to the World Health Organization (WHO), seizure episodes are a conclusion of excessive electrical discharges in a group of brain cells. These discharges can emerge in several parts of the brain. The frequency of seizures caused by these discharges can range from 1 per year to several per day (<https://www.who.int/en/news-room/fact-sheets/detail/epilepsy>, accessed on 16.12.2020). Epilepsy can be described as any of the following circumstances according to the International League Against Epilepsy (ILAE) classification:

- 1- At least 2 times to provoke the occurrence of seizure in 1 day
- 2- Seizure occurring in the next 10 years and their probability (having at least a 60% chance of seizures)
- 3- Diagnosis of epilepsy syndrome (Beghi, 2020; Fisher et al., 2014)

2. Pathology of Epilepsy

The fundamental mechanism of epileptic seizures is extreme and unusual electrical activity in the cortex (Fisher et al., 2005). This pathological situation in the brain can be seen in different regions such as temporal, frontal, parietal, and occipital-lobe (Aronica and Mühlebner, 2017; Kwan et al., 2011). Although the pathology of epilepsy is not yet exactly known, several reasons are thought for the disease. In addition to reasons such as brain damage, stroke, brain tumors, brain infections, or birth defects (Fisher et al., 2005), genetic mutations are thought to play a serious role in the occurrence of the disease (Pandolfo, 2011). Epilepsy studies due to genetic factors are still ongoing. For example, according to the isolation results of samples taken from patients with infantile-onset seizures, it is thought that the disease may be caused by a mutation in the PCDH19 gene (Hynes, 2010). Also, cerebrovascular disorders, defects of cortical development, metabolic diseases are associated with epilepsy pathology (Kwan et al., 2011).

3. Diagnosis of Epilepsy

Diagnosis should be based on anamnesis whether the person had an epileptic seizure, the description of the attack, and the combination of different symptoms. Electroencephalography (EEG), long-term video electroencephalography (EEG), high-resolution MRI, neurophysiological tests are essential tests for the diagnosis. Today, EEG plays an important role in the non-invasive diagnosis of epilepsy. EEG is the most important auxiliary diagnosis method besides the anamnesis and EEG should be performed on every patient

who is thought to have a seizure. Information about deep brain functions and pathological processes is provided with EEG and video EEG (Reif et al., 2016). Existing methods for the detection of seizures use simulations for feature extraction from EEG signals. Epileptic findings are evaluated with stimulants given during EEG (Ullah et al., 2018). For this reason, flash stimulants in the EEG used in diagnosis are among the important factors that trigger seizures. Optional methods include PET and SPECT, functional MR, MR spectroscopy, magnetoencephalography, and Wada test (Ergun et al., 2017). MR method is used to define the seizure onset regions (Ryvlin and Rheims, 2012). Nuclear Medicine Tests SPECT and PET are nuclear medicine imaging methods used to identify the epileptic focus before surgery. Radiopharmaceuticals used for SPECT are Tc-99m HMPAO and Tc-99m ECD. The mostly used radioactive material for PET imaging is F-18 FDG, and F-18 flumazenil (FMZ) also shows the seizure area, even localized in a more limited area than FDG (Yalnizoglu et al., 2012). Neuroimaging can be used to reveal structural abnormalities that may be the cause of epilepsy. Magnetic resonance imaging (MRI) is the preferred imaging study. MRI method can be used in patients who show a focal onset in any way with the patient's history, symptoms on examination, or EEG (Kinay, 2012).

4. Epilepsy Treatment

In individuals diagnosed with epilepsy, it is very important to determine the seizure type, seizure frequency, and recurrence risk. Treatments aim to eliminate seizures or to reduce the frequency of seizures and to increase the patient's quality of life (Erdinç, 2013; Rowland, 2008). Antiepileptic drugs are frequently used in the treatment. Drug resistance is one of the major challenges in the treatment (Télliez-Zenteno et al., 2014). However, the likelihood of disease recovery is reduced due to drug resistance. In addition to drug therapy, alternative treatment methods continue to be developed. One of these methods is epilepsy surgery. Surgery could be a choice for focal seizures to control the seizures completely. Vagus nerve stimulation, anterior thalamic stimulation, and stimulation responsive to the closed-loop are the three types of surgery that can be performed for individuals who do not respond to medications (Edwards et al., 2017). Other alternative treatment methods include vagus nerve stimulation (Yuan and Silberstein, 2016), deep brain stimulation (Kwon et al., 2018), responsive neurostimulation (Skarpaas et al., 2019), and the ketogenic diet (Liu et al., 2018). However, the drugs used in the treatment of epilepsy are supportive treatments and the healing effect of the disease is very low. Although the effects on the frequency of seizures have been observed in alternative methods, these methods need to be improved. Antiepileptogenic agents to prevent epilepsy before the first seizure in at-risk patients and disease-modifying new agents to control ongoing severe epilepsy associated with progressive underlying disease are also needed (Schmidt and Schachter, 2014).

5. Nanotechnology for Delivery of Drugs: Nano-carrier Systems

Nano-carrier systems as drug delivery systems have become one of the prominent research topics with the development of nanotechnology. Nano-carrier systems are seen as a new generation therapy with the targeted delivery of therapeutic small drug molecules and genes to cells specific (Ding and Li 2017; Farokhzad and Langer, 2009). Nano-carriers have two main advantages. First, nano-carriers have a larger

surface-to-volume ratio so they contribute to a significant reduction in drug concentration. As the dose decreases, the side effects and toxicity of the drug will decrease (Zhang et al., 2016). Second, drugs can be targeted to a specific tissue. Thus, the drug effect is further increased (Liu et al., 2016).

It can take on more than one task with the nano-carrier system. Several of these tasks, therapeutic drug can be included in the nano-carrier system or the drug surface can be encapsulated. It is thought that nano-carrier systems can be effective in diagnosing diseases as well as their therapeutic effectiveness (Fan et al., 2016).

There are many different forms of nano-carriers. For example, these nano-carrier systems are nanocarbon, polymeric nanoparticles (PNPs), solid lipid nanoparticles (SLNPs), nanocolloids, liposomes, aerogels, and micelles. However, recent studies have shown that nanosystems, such as dendrimers, nanoemulsions, nanogels, nanosuspensions, and nanotubes, have been developed. Nano-carrier systems have very small dimensions. The dimensions of nano-carrier systems designed with nanotechnology can vary between 1 and 500 nm. (Alexander et al., 2019; Bonferoni et al., 2019). To compare nano-carrier systems, the average size of cells is 10–20 μm , while the least diameter of blood capillaries is 6–9 μm . It has been found that the dimensions of nano-carriers are quite small compared to the sizes of human cells. Thus, nano-carriers are easily transported and absorbed by brain capillary endothelial cells by the mechanism of endocytosis and transcytosis transport (Vilella et al., 2014).

6. Nano-Carrier Drug Systems in the Treatment of Epilepsy

In recent years, CNS diseases are one the most common causes of death and disorders in the world. In the treatment of these diseases, complexities such as the inability of improved formulations to pass through the BBB, limited neuroregeneration, and inadequacy to remove the disease factor from the environment are experienced (Feigin et al., 2019). Nanotechnological research developing in recent years has shown that the nanomaterials can cross via the BBB and that the development of new treatment approaches for CNS diseases has also been a gleam of hope. Nanotechnology-based drug delivery is well novel as compared to classic treatment methods and an encouraging approach in the field of neurological disorders as nano-carriers have been demonstrated powerful in fascinating traversing the BBB or blood-cerebrospinal fluid barrier and so active delivering drugs (Li et al., 2017; Poovaiah et al., 2018).

Current knowledge has shown that nanomaterial systems have revolutionized the treatment of various CNS diseases. It has been observed that it has the potential to treat diseases such as Parkinson's and Alzheimer's diseases, stroke, as well as brain tumors and epilepsy.

Different strategies have been developed for epilepsy treatment, however, the nanotechnological research has shown excellent potential to overcome all major obstacles in epilepsy treatment. In a 2012 study, it has been observed that the formulation obtained with carbamazepine intranasal mucoadhesive nanoemulsion (MNEG) targets the brain and significantly prolongs the onset of convulsion in convulsive rat (Samia et al., 2012). In another study, it is reported that-carotene loaded PLGA nanoparticles have a greater anticonvulsant effect compared to polysorbate-80 coated carotene nanoparticles (Yusuf et al., 2012). It has been observed that the formulation formed in the encapsulation of hydrophobic drug molecules with

bioactive nanomaterials and biodegradable polymeric materials has effective bioavailability. It was observed that the formulation obtained with the piperine-loaded hyaluronic acid (HA)/Poly (lactico) encapsulated Copper oxide quantum dots delayed myoclonic jerks (MCJ) (Zhu et al., 2020). In an experimental study on mice with an epilepsy model derived from Scn1a, it was reported by researchers that nanoparticle-encapsulated oxytocin robust and sustained protection against induced seizures and improved social behavior (Wong et al., 2020). Other studies on this subject are shown in Table 1.

Table 1. Nano-carrier systems developed for epilepsy treatment

Nano-carrier system used	Antiepileptic drug used	Results	Reference
Nanostructured Lipid Carriers	Carbamazepine (CBZ)	Carbamazepine loaded nanostructured lipid transporters (CBZ-NLC) has better brain transmission and therapeutic results compared to CBZ	Khan et al., 2020
	Oxcarbazepine (OXC)	The formulation obtained by encapsulating Oxcarbazepine in nanostructured lipid carriers (NLCs) consisting of cetyl palmitate and oleic acid coated with polyvinyl alcohol (PVA) or chitosan (Ch) was found to remain in the circulation longer than Oxcarbazepine alone.	Scioli Montoto et al., 2021
Nanoliposome	Lamotrigine (LTG)	In particular nasal delivery Lamotrigine-Nanoliposome (LT-GNP) to the brain compared to LTG is therapeutically effective	Praveen et al., 2019
Solid Lipid Nanoparticles	Carbamazepine (CBZ)	Carbamazepine loaded Solid lipid nanoparticles (CBZ-SLN) being protected against seizures	Scioli Montoto et al., 2018
	Curcumin	It has been observed that the formulation obtained by encapsulating curcumin with solid lipid nanoparticles reduces neuronal apoptosis.	Huang et al., 2020
Polymeric Micelles	Clonazepam (CLZ)	Clonazepam (CZ) loaded polymeric micelles (PM) have a protective effect against seizures, especially in emergency treatment for status epilepticus	Nour et al., 2016

Transferosomes	Clonazepam (CLZ)	The formulation developed with clonazepam (CZ) transferosomes has a protective effect against seizures, especially in emergency treatment for status epilepticus	Nour et al., 2017
Polymeric Nanoparticles	Carbamazepine (CBZ)	Carbamazepine loaded carboxymethyl chitosan nanoparticles (CBZ-NPs) have a significant effect, especially in targeting the brain	Liu et al., 2018
	Oxcarbazepine (OXC)	Oxcarbazepine (OXC) loaded PLGA NPs reduced the number of administrations to 1 over 24 h compared to the free drug thus controlling seizures in rats.	Musumeci et al., 2018
	Thyrotropin-releasing hormone (TRH)	<i>In vitro</i> studies showed that the formulation obtained by encapsulating the TRH analogue with PLGA could be an active nano-carrier system.	Kaur et al., 2018

With all this information, it has been observed that the different antiepileptic drugs used are effectively transported to the brain by nano-carrier systems. It is thought that nano-carrier systems may be a new treatment strategy in many CNS disorders, especially in epilepsy.

Conclusion

Epilepsy is a chronic neurological disorder. Many mechanisms underlying the disorder remains a mystery. Besides, the quality of life of the patients is decreasing day by day due to seizures characterized by the disease. Although EEG has been the preferred diagnostic method frequently, the development of imaging methods for the brain is important especially for early diagnosis. Nowadays, there are several treatment options available to reduce the period and frequency of seizures of epilepsy. However, the patient still must struggle with this disease for life. Overall, new approaches are needed in the treatment of other CNS diseases, especially epilepsy. With the recent studies and the development of nanotechnology, it is thought that it is efficient in the treatment of epilepsy compared to classic treatment methods. Designed nanomaterials have perfect advantages owing to their properties such as increasing biocompatibility, increasing blood circulation time, and reducing systemic toxicity, targeting specifically to the region, and

continuous and controlled drug release. However, studies on epilepsy treatment of nano-carrier systems are limited and further studies are needed. Drug delivery systems designed with nanomaterials should be investigated by conducting preclinical studies. We think that it is possible to treat epilepsy with nano-carrier systems.

Conflict of Interest

No conflict of interest is declared by the authors.

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Industry 4.0 Elements for Pharmaceutical Development and Manufacture



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Abstract: The innovations of the Industry 4.0 revolution in the New World aim at creating a society where we can solve many problems in every sector and social life. As a condition for Industry 4.0, industrial sectors are heading towards digitalization and automation. Pharmaceutical Industry takes its share in this sense and tries to keep up with this pace in the context of Pharma 4.0 which is a hot topic. However, it is a known fact that developing safe and effective new treatments is a long, difficult, and expensive process, so FDA released the Pharmaceutical cGMPs for the 21st-century report and in this report; it specified Quality by Design (QbD) and Process Analytical Technologies (PAT) initiative to bring a solution. The introduction of the new QbD approach, which advocates providing the quality within the product with design instead of testing, brought an increase in the quality of the products manufactured, a decrease in costs and accelerated the market launch of the medicines. Moreover, patient safety is brought to the fore with better quality medicines and the patient accesses the drug in a shorter time.

Keywords: Industry 4.0; pharma 4.0; QbD; PAT; pharmaceutical development; pharmaceutical manufacture

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1. Introduction

The reform that started the industrial revolution with the English engineer Thomas Newcomen developing a machine to drain water in 1712 is now called Industry 1.0. With the discovery of electricity and its use as a power supply, the concept of Industry 2.0 emerged, and the manufacture of automobiles started. The dominance of the digital and electronic systems and information systems in the sector accelerated mass production and increased automation over time. Thus, the third industrial revolution started, and more precise, efficient, and good standards were produced thanks to computer-controlled production. With Industry 4.0 that came later, the importance of manpower became lost, cyber and physical systems came into play and the factories started to use concept of Internet of things. These physical systems made the management of factories much easier, decreased energy consumption and increased efficiency.

The innovations of the Industry 4.0 revolution in the New World aim at creating a society where we can solve many problems in every sector and social life. Thus, the future society is planned to be a super smart society where new values and services are created constantly and life is easier and more sustainable.

2. Pharma 4.0 concept

As a condition for Industry 4.0, industrial sectors are heading towards digitalization and automation. Pharmaceutical Industry takes its share in this sense and tries to keep up with this pace in the context of Pharma 4.0 which is a hot topic. The Pharma 4.0 concept promises enhanced opportunity in terms of product safety and security through digitalization, data analysis technology, Internet of Things (IoT), continuous manufacturing and artificial intelligence technology (Kumari, 2020).

Implementation of adaptive and innovative technologies from Industry 4.0 revolution will lead to establish more robust and agile production processes characterized by fewer interruptions and defects, with higher quality management levels for pharmaceutical companies. Integration of Industry 4.0 elements will also upgrade the pharmaceutical production plant to a “reconfigurable factory” which may provide mass customization of personalized drugs for different demands. Effective knowledge web across company boundaries and big data analytics can improve process monitoring performance and achieve sustainability with reducing material waste, overproduction, and energy consumption (Reinhardt et al., 2021).

3. Quality by Design (QbD) and Process Analytical Technology (PAT)

It is a known fact that developing safe and effective new treatments is a long, difficult and expensive process, so FDA released the Pharmaceutical cGMPs for the 21st-century report and in this report, it specified Quality by Design (QbD) and Process Analytical Technologies (PAT) initiative to bring a solution. The introduction of the new *QbD* approach, which advocates providing the quality within the product with design instead of testing, brought an increase in the quality of the products manufactured, a decrease in costs and accelerated the market launch of the medicines. Moreover, patient safety is brought to the fore with better quality medicines and the patient accesses the drug in a shorter time (Aksu, 2013).

As specified in the International Conference on Harmonization (ICH) Q8 guidelines, QbD is a systematic drug development approach that begins with predefined goals and emphasizes understanding of the product and process based on sound science and quality risk management (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2009). QbD increases knowledge on the process and helps to better understand the product, which often happens through the application of new technologies such as PAT or modelling. It enables pharmaceutical development, production and quality assurance by advocating risk-based approaches based on science and scientific data and can be considered is one of the drivers of Pharma 4.0.

Recent regulatory measures on pharmaceutical quality, such as Process Analytical Technology (PAT) Guidance by the FDA, the draft Process Validation Guidance recently released by the FDA and ICH Guidelines (Q8, Q9 and Q11), have all encouraged the use of advanced PAT technologies and QbD principles with the

aim of gaining in-depth process understanding, reducing, and eliminating the risk of releasing poor or substandard quality pharmaceutical products to the public (Wu and Khan, 2010).

QbD involves the integration of six main steps: Quality Target Product Profile (QTPP), process and product design risk assessments, DOEs, design space, control strategy, and continuous process improvement. Together with PAT tools, these cover the entire manufacturing process from the beginning to the end of the manufacturing chain along with logistics and business planning and have sought to understand processes in development over the past decade by gathering and analyzing data using multivariate data analysis methods and developing effective monitoring and control systems. They also provide a basis for the design of pharmaceutical products and manufacturing processes, thus making the products acceptable and affordable and the production lines more reliable without quality failures. If PAT and QbD approaches are used at any stage of production to assure the material and product quality, real-time release testing (RTRT) can be realized. Real-time release testing means the capability, based on process data provided by in-line, non-destructive analytical sensors, to assess and ensure the appropriate consistency of the in-process and/or final product, thus providing commercial and economic benefits for the manufacturers like decreasing in end-product release testing and removing of superfluous manufacturing scale monitoring and control (Kessler and Kessler, 2020; Mészáros et al., 2020; Shah et al., 2011).

When PAT tools such as chemometric tools, process analysers, endpoint tracking tools and information management tools are combined, the production process can be actively and adaptively controlled; also decrease in cycle times with the utilization of on-, in-, or at-line measurements and controls, elimination of raw material waste (e.g. chemicals and high-quality water), release of the products in real time, and expanded use of automation are expected to contribute to improved quality and efficiency (Shah et al., 2011).

Despite the financial result and competitive interests obtained by various industries that adopt process analytics, pharmaceutical companies are restricted in their efforts to implement PAT. The various factors restricting the implementation of PAT that have caused the current state and can be summarized into three categories: real and perceived technological barriers since the process control requires a high level of automation and highly robust sensors that can survive the industrial environment, lack of economic incentives and factors hindering licensing should be considered (Cogdill, 2008; Kessler and Kessler, 2020).

3.1. Data Analysis

Data analysis methodologies are also among the important QbD tools. The expanded opportunities offered by on-line/in-line/at-line PAT process analysers and material sensors progressed significantly in last 15 years used to track any specific process or material produces significantly large and complex data sets. Thus, advanced data management techniques are required for the intricacy of such complex data analysis. By using appropriate techniques including Multi Variate Data Analysis (MVDA) in the analysis of these real-time dynamic process data, we can extract material characterization, critical product/process information and knowledge, and this is essential for rationale product and process design, and process control. In addition, machine learning (ML) and deep learning (DL) principles, can infer the model function from

sample input results are used to explain the behaviour of the system instead of using physic / engineering or chemometric based models, offer new approaches to designing complex system or data-driven systems models in Industry 4.0 applications (Kessler and Kessler, 2020; Stagner and Haware, 2019; Wu et al., 2011).

4. Digitalization in the Context of Pharma 4.0

In terms of digitalization, Industry 4.0 concept includes cyber-physical systems (CPS), the internet of things (IoT), industrial internet of things (IIOT), cloud computing, 2 cognitive computing and artificial intelligence to optimise all aspects of processing over the entire product life cycle (Vaidya, 2018).

Further digitalization, the basis for the Industry 4.0 will dramatically change the structures of future development enabling the connectivity and cloud services and advanced data analysis tools which allows experts to extract and analyze enormous amount of information (*i.e.*, big data) from the supply chain, products, machines, and production lines; then the realization of Cyber-Physical Systems (CPS) that is managed or monitored by computer-based algorithms that are embedded into the Internet structure and needs a combination, respectively between physical and computational elements for the process industry (Kessler and Kessler, 2020; Reinhardt et al., 2020; Reinhardt et al., 2021).

Conclusion

It is an indisputable fact that the contributions of Industry 4.0 to healthcare technology will provide numerous benefits in the future. The relationship between technology and the healthcare sector today is evident in the establishment of health information systems in healthcare institutions to collect, store, share, transmit and manage medical data of individuals or data related to various processes.

To conclude, even though further research and a clear roadmap for execution in Pharma 4.0 is required to increase the knowledge, the implementation of Industry 4.0 to the pharmaceutical industry is promising to bring new opportunities, which can solve the problem of efficiency in manufacturing, more robust process and R&D growth, data evaluation.

Conflict of Interest

Authors declare no conflict of interest.

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Instruction for Authors

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Introduction; 6. Materials and Methods; 7. Results 8. Discussion; 9. Conclusion; 10. Acknowledgement; 11. Conflict of Interests; 12. References. Manuscripts submitted as a "Research article" do not have a wording limit. However, manuscripts that are submitted as "Research article" should be more than 5000 words, excluding the tables, figures and references.

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Preparation of manuscript and general rules

The manuscripts should be written double spaced in Arial font type and 12 pts font size. Each page should be numbered, and consecutive line numbers should be provided. Title page, authors list and affiliations should be prepared as a separate file. Tables and Figures should also be prepared as a separate file.

Title Page: The title page should contain the full title of the work which should not exceed 200 characters. Abbreviations should be avoided in the title. Main title of the manuscript should be followed by the "short title" which should not be longer than 70 characters. Short title should be followed by the list of author names. Author names should be given as name and surname followed by superscript Arabic numbers indicating the affiliations. One author should be designated as the corresponding author and should be indicated in the authors list with the superscript asterix symbol after the affiliation indicator. Author list should be followed by the list of affiliations which indicate the department, institution, postal code, city, country and e-mail(s) of the author(s). Finally, corresponding author full mailing address, telephone, fax and e-mail should be provided. Acknowledgement and Conflict of Interests parts should be given in the title page.

Main text: Main text should be divided into sections and sub-sections using Arabic numerals, starting from the introduction part. Sections should be indicated with bold and non-italic characters. Sub-sections should be indicated with bold and italic characters (as given in example).

Section Example: 1. Introduction

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First page of the main text should contain the title followed by a 300-word abstract. Abstract should not contain citations. Abbreviations could be used in the abstract however; full explanation of the abbreviations should be given at the first time that they have appeared in the abstract. Abstract should briefly summarize the study. Abstract should contain the following information: 1. Purpose/Aim of the study; 2. Materials and methodology used in the study; 3. Key results obtained in the study; 4. Conclusion remarks. Abstract part should be followed by 6 keywords that describe the work. Keywords should be separated from one another with a semicolon.

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Acknowledgement

Authors should indicate any acknowledgement related to the study in this part.

Conflict of Interests

Authors should clearly indicate any kind of conflict of interests for the study in this part. If the authors do not have any conflict of interests, they should indicate "Authors declare no conflict of interests".

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The authors should indicate the position of Tables and Figures in the text by indicating the Title of the table (as given in the example). All figures should be provided as a tiff file with at least 300 dpi resolution. The images given as figures should be authentic, no manipulations should be done. Color figures are welcome in the journal and does not require a publication fee.

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Cited references which have the same first author(s) that were published in the same year: (last name of the author, year of publication and uncapitalized letters for separation)

Example: (Biyikoglu, 2017a; Biyikoglu, 2017b)

Cited references as lists: The references that are going to be given as a list in a single parentheses should be first arranged alphabetically than chronologically.

Example: (Biyikoglu 2017a; Biyikoglu 2017b; Polatoglu et al., 2013)

Cited references given in text: If author names are going to be mentioned in the text for the citation than it should be given as: "...Polatoglu et al. (2013)....."

Examples: ".....Polatoglu et al. (2013) have indicated...."

".....Biyikoglu (2017) demonstrated that....."

Reference formatting

The reference formatting should be given according to the following style (APA7). DOI numbers should be given after the reference if available.

Reference style

Reference to a journal publication:

Polatoğlu, K., Demirci, F., Demirci, B., Gören, N., Baser, K. H. C. (2010). Antibacterial activity and the variation of *Tanacetum parthenium* (L.) Schultz Bip. essential oils from Turkey. *Journal of Oleo Science*, 59(4), 177-184. <https://doi.org/10.5650/jos.59.177>

Reference to a book:

Preedy, V. R. (Ed.). (2015). *Essential oils in food preservation, flavor and safety*. 1st Ed., Academic Press, Elsevier, Oxford, UK.

Reference to a chapter in an edited book:

Polatoğlu, K., Karakoç, Ö. C. (2015). Biologically Active Essential Oils against Stored Product Pests. 1st Ed., In Preedy, V.R. (Eds.), *Essential Oils in Food Preservation, Flavor and Safety*. Academic Press, Elsevier, Oxford, UK, pp. 39-59.

Reference to a website:

National Cancer Institute, A success storyTaxol® (NSC 125973) https://dtp.cancer.gov/timeline/flash/success_stories/s2_taxol.htm (accessed 14 December 2017)

Reference to a Thesis:

Knight, K.A. (2011). *Media epidemics: Viral structures in literature and new media* (Doctoral dissertation).

Abbreviations

Full explanation of the abbreviations should be given at the first time that they have appeared in the text. Title should not contain any abbreviations. After the explanation of the abbreviations are given in the text authors could use abbreviations throughout the text.

Example: ".....Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes were"

Chemical and Biological Nomenclature

The names of the biological organisms should be given in full of the author name at the first time they appear in the text. The genus and species names should always be written in italics. Authors could use the short name of the organism after the full name was indicated. Local names of the organisms could be mentioned however, throughout the manuscript these organisms should be referred to with their binominal names.

Chemical compounds should be preferably named according to the IUPAC nomenclature.