DOI: 10.5455/bcp.20120412022107

Descriptive Features of Depressive Disorder Patients with who Have Committed Suicide by Drug Overdose

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ÖZET:

Adli Tıp Kurumu'nca incelenen ilaçla intihar eden depresif bozukluk tanılı hastaların tanımlayıcı özellikleri

Amaç: Depresif bozukluk tanılı ilaçla intihar eden olguların hangi tür ilaçları ne şekilde aldığı ve yaklaşık olarak ne kadar süre sonra öldüklerini ortaya koymak amaçlandı.

Yöntemler: İlaçla intihar ettiği tespit edilen aynı zamanda major depresyon hastası olan ve otopsilerinde içtikleri ilaca ait etken madde bulunan 13 kadın ve 18 erkek toplam 31 olgu çalışmaya dahil edildi. Her bir otopside tespit edilen ilaçlar; "yalnızca antidepresan içerenler", "hiç antidepresan içermeyenler" ve " en az bir antidepresan ilaçla birlikte diğer grup ilaçlardan en az birini içeren (karışık)" olmak üzere 3 grupta ele alındı. Otopsi sonuçlarına göre olguların kan, idrar ve/veya vücut dokularında 35 çeşit ilaç tespit edildi. İntihar amaçlı kullanılan 35 çeşit ilacın tekli, ikili, üçlü, dörtlü, beşli ve altılı kombinasyonlar halinde kullanıldığı tespit edildi. 31 olgu içinde yalnızca 4 olguda 4 ve daha fazla sayıda ilaç kombinasyonu vardı. Bu yüzden istatistiksel olarak değerlendirme yapılırken ilaç kombinasyonları; "Tekli", "İkili" ve "≥ 3'lü" olmak üzere 3 farklı şekilde ele alındı.

Bulgular: Her iki cinsiyette de antidepresan içermeyen grupla intihar sayısı fazladır. Ancak ilaç gruplarına göre cinsiyetler arasında istatistiksel olarak anlamlı farklılık bulunmamaktadır. Tek ilaçla ve ikili kombinasyonlarla intiharlarda daha çok antidepresan içermeyen grup tercih edilmiştir. ≥ 3'lü kombinasyonlarda daha çok hem antidepresan içeren hem de antidepresan olmayan ilaçları içeren yani karışık grup tercih edilmiştir. İlaç gruplarına göre ilaç kombinasyonları arasında istatistiksel olarak anlamlı farklılık bulunmaktadır (p=0,05). Onaltı olgu aynı gün içerisinde ölü bulunmuş, 15 olgu ise yoğun bakım tedavisi gördükten sonra ölmüştür. Yalnızca antidepresan içeren grupla intihar eden olgularda aynı gün içerisinde ölü olarak bulunanların sayısı, yoğun bakım tedavisi gördükten sonra ölenlerin sayısından fazladır. Ancak ilaç gruplarına göre ölüm zamanları arasında istatistiksel olarak anlamlı farklılık bulunmamaktadır.

Sonuç: En sık veya en öldürücü zehirlenmeye neden olduğu gözlenen ilaçların daha sıkı denetim ve gözetimle kontrol altında tutulması gerekmektedir. Aydınlatılmış onam alınırken nasıl ki ilacın terapötik dozdaki etkileri anlatılıyor ise, ilaç paketindeki ilaçların tamamının tek seferde alındığı taktirde nasıl sonuçlar doğuracağı konusunda da hastanın bilgilendirilmesi gerekmektedir. Depresyon hastalarına ilaçları kutu halinde verilmeyip sınırlı sayıda verilebilir. Bu durumda diğer ilaçların da gerekirse şifreli kasada saklanması gerekmektedir. Diabet hastalarının depresyona girip girmediği konusu da ayrıca yakından takip edilip değerlendirilmelidir.

Anahtar sözcükler: Depresyon, ilaç, tamamlanmış intihar, toksisite

Klinik Psikofarmakoloji Bülteni 2013;23(2):155-61

ABSTRACT:

Descriptive features of depressive disorder patients with who have committed suicide by drug overdose

Objective: The goal of this study was to determine the drugs of choice, the preferred routes of administration and the time to death among depressive disorder patients who have committed suicide by drug overdose.

Methods: Thirty-one patients were included in this study, 13 females and 18 males, who had committed suicide by drug overdose, had a major depression, and had active drug substances detected in post-mortem samples. The drugs detected after autopsy were categorized into 3 groups: "containing only anti-depressant", "containing other than anti-depressant" and "containing a mixture of anti-depressant(s) and drug(s) of another ATC class". According to the results of the autopsies, 35 kinds of drugs were found in post mortem samples of blood, urine and/or tissues. The 35 kinds of drugs used for suicide were found to be used either solely or as a combination of 2 to 6 different drugs. Only 4 cases out of 31 had cocktails of 4 types or more. Thus, we categorized the combinations of drugs during the statistical evaluation in three classes as "single", "duo" and "three or more (≥ 3)".

Results: In both sexes, the number of suicides was higher in the "containing other than anti-depressant" group. However, there was no statistically significant difference between the genders according to drug groups. The "containing other than anti-depressant" group of drugs was preferred as a "single" or "duo" combination. The "containing a mixture of anti-depressant(s) and drug(s) of another ATC class" group was preferred as a "three or more ≥ 3" combination. There was a statistically significant difference between the drug combinations in reference to drug groups (p=0.05). Sixteen patients were found dead on the same day as the overdose and 15 patients died after intensive care treatment. Among the patients who committed suicide by using a member of the "containing only anti-depressant" drug group, the number of patients who were found dead on the same day as the overdose was more than the number of patients who died after intensive care treatment. However, there is no statistically significant difference between drug groups in reference to the time to death.

Conclusion: The most common or most lethal drugs that cause intoxication should be stringently controlled. When the effects of therapeutic doses are explained during informed consent, the patients should be informed about the consequences when drugs are taken concomitantly. Patients with a depression diagnosis can be dispensed medications in counted unit doses, instead of the whole box. In this case, the remaining part in the box should be kept in a safe place with restricted access for the patient, if necessary. Patients with diabetes should also be closely observed and evaluated for depression.

Key words: Depression, drug, completed suicide, toxicity

Bulletin of Clinical Psychopharmacology 2013;23(2):155-61

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Gönderme tarihi / Date of submission:
24 Kasım 2011 / November 24, 2011

Kabul tarihi / Date of acceptance:
12 Nisan 2012 / April 12, 2012

Bağıntı beyanı:
M.N.K., E.K., M.B., G.B., O.D., M.E., H.T.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
M.N.K., E.K., M.B., G.B., O.D., M.E., H.T.: The authors reported no conflict of interest related to this article.

OBJECTIVE

Drugs, which are used to treat physiological disorders or diseases, can show the intended biological efficacy only within a certain dose range (therapeutic dose). When given above the higher limit of therapeutic range, toxic effects (at toxic doses) and lethal effects (at lethal doses) are seen. Every drug can be toxic under certain conditions. The therapeutic index is generally used by comparing the therapeutic and toxic doses of a drug. A drug is considered safer when the therapeutic index is higher (1).

Affective disorders, and particularly mood disorders, are among the psychiatric disorders with the highest risk of suicide. Successful suicide is almost 30 times more common among individuals experiencing depressive disorder (2). Individuals working in the psychiatry field observe that, in clinical studies, suicidal thoughts are decreased along with depressive symptoms with antidepressant treatment. However, it has also been emphasized that under some conditions, antidepressants may possibly induce or increase suicidal ideation and suicidal behaviors (3). Suicidal attempts are frequently performed by ingesting drugs, particularly benzodiazepines, antidepressants and/or barbiturates (4). A study conducted in our country revealed that the most common (65.5%) method of suicidal attempts was to take in toxic doses of drugs normally intended for medical treatment (5). In the present study, we retrospectively investigated the characteristics of patients, who committed suicide by ingesting drugs, which resulted in death, in the last two years.

MATERIALS AND METHODS

For our study, we investigated retrospectively, the autopsy reports conducted in 2010-2011 at the Council of Forensic Medicine. Forty-eight out of 141 subjects, who died due to intoxication were identified as suicide with drugs. A total of 31 subjects, 13 females and 18 males, who were identified as suicide cases who had suffered from major depression and had active drug substance(s) detected during autopsy, were included in the study after ethics committee approval. Seventeen subjects were excluded since they did not meet one or more of the inclusion criteria. Since some of the subjects had been in intensive care treatment, lethal drug doses were not determined in all subjects. However, the confirmed cause of death was drug intoxication in all subjects. Anaphylactic reaction was not observed in any subject. The agent was taken orally in all subjects.

Two different age groups ("<30 years" and "≥30 years") were used when evaluating the subjects. In each autopsy, the drugs identified were classified into three groups: "including only antidepressants", "no antidepressants", "at least one antidepressant combined with at least one drug from another ATC class (mixed)". According to autopsy results, 35 types of drugs were identified in the blood, urine and/or body tissues of the subjects. We found that, to commit suicide, depressive patients used these 35 drugs as the sole agent or a combination of two to six different drugs. During statistical analysis, drug combinations were taken as three different groups: "single", "duo", and "≥3". These three different combinations were compared statistically with the three different groups: "including only antidepressants", "no antidepressants" and "at least one antidepressant combined with at least one drug from another ATC class (mixed)". The groups were also evaluated for age and gender. In addition, statistical analyses were conducted in consideration of the existence of intensive care treatment or not.

When the subjects who committed suicide by taking a single drug were taken into account, three subjects took metformin (527.78 µg/ml, 963.157 µg/ml and 216 µg/ml, respectively), one took pentobarbital (30.5 µg/ml), and one took fentanyl (0.144 µg/ml). In particular, suicide attempts with drugs which are used in psychiatry practice were investigated; two subjects took benzodiazepines (37.753 µg/ml and 40.69 µg/ml, respectively), one took amytriptiline (11.78 µg/ml), one took quetiapine (38.9 µg/ml), one took valproic acid (446 µg/ml), one took hydroxyzine (11.859 µg/ml), one took citalopram (0.892 µg/ml), and one took carbamazepine (30.5 µg/ml) to commit suicide.

In the group of 10 subjects, who committed suicide by taking a combination of two drugs, the following drug combinations were used: maprotiline (8.108 µg/ml) & clomipramine (1.919 µg/ml), doxylamine (1.45 µg/ml) & chlorpromazine (0.98 µg/ml), hydroxyzine (23.033 µg/ml) & ethanol (2150 µg/ml), verapamil (1.1164 µg/ml) & quetiapine (7.47µg/ml), amitriptyline (1.208 µg/ml) & nortriptyline (0.364 µg/ml), tianeptine (0.9566 µg/ml) & mirtazapine (0,368 µg/ml), propofol (5,447 µg/ml) & atrocorium (0,125 µg/ml), midazolam (0.351 µg/ml) & lidocaine (32.86 µg/ml), nordiazepam (66.42 µg/ml) & diazepam (61.08 µg/ml), verapamil (0.164 µg/ml) & quetiapine (7.47 µg/ml) drug combinations.

Four subjects who committed suicide by taking a combination of three drugs were identified; chlorpheniramine (0.343 µg/ml) + lidocaine (0.520 µg/ml) + dipyrone (0.117 µg/ml), biperiden (0.973 µg/ml) + clomipramine (0.187 µg/ml) + sertraline (1.314 µg/ml), amitriptyline (1.209 µg/ml) + nortriptyline (0.667 µg/ml) + carbamazepine (84.00 µg/ml), chlorpromazine (10.00 µg/ml) + biperiden (0.474 µg/ml) + ethanol (206 µg/ml).

When the two subjects who committed suicide by taking a combination of four drugs were investigated, we found that they took the following combinations: citalopram (0.172 µg/ml) & sertraline (0.162 µg/ml) & alprazolam (0..87 µg/ml) & quetiapine (58.1 µg/ml); olanzapine (0.595 µg/ml) & fluvoxamine (0.220 µg/ml) & fluoxetine (0.787 µg/ml) & clomipramine (1.320 µg/ml).

One subject committed suicide by taking a combination of five drugs: diazepam (140 µg/ml) & pentobarbital (94.0 µg/ml) & quetiapine (1.90 µg/ml) & phenytoin (0.324 µg/ml) & valproic acid (0.60 µg/ml).

One subject committed suicide by taking a combination of six drugs: amitriptyline (6.77 µg/ml) & nortriptyline (2.550 µg/ml) & mianserin (0.415 µg/ml) & sertraline (0.206 µg/ml) & citalopram (1.420 µg/ml) & metoclopramide (1.150 µg/ml) (Table 1).

NCSS (Number Cruncher Statistical System) 2007 software was used for statistical analysis. Chi-square test and Fisher's exact chi-square test were used to compare qualitative data. Results were reported to be statistically significance at $p<0.05$ with a 95% confidence interval.

RESULTS

The study was conducted in 2010-2011 with a total of 31 subjects, including 13 (41.9%) females and 18 (58.1%) males.

The youngest subject was 16 and the oldest was 82 years old. When gender distribution according to age groups were investigated; there were 4 females (57.1%) and 3 (42.9%) males under 30 years old and 9 (37.5%) females and 15 males (62.5%) over 30 years old (Table 1).

Table 1: Gender Distribution According to Age Groups

Gender	Age Groups	
	<30 years of age N (%)	>30 years of age N (%)
Female	4 (57.1%)	9 (37.5%)
Male	3 (42.9%)	15 (62.5%)

When gender distribution according to drug groups was examined, it was evident that the distribution between the drug groups was similar in females (including only antidepressants 40%; no antidepressants 42.9% and mixed group 40%) and males (including only antidepressants 60%; no antidepressants 57.1% and mixed group 60%) (Table 2).

Table 2: Gender Distribution According to Drug Groups

Gender	Including Only Antidepressants N (%)	No Antidepressants N (%)	Mixed N (%)
Female	2 (40%)	9 (42.9%)	2 (40%)
Male	3 (60%)	12 (57.1%)	3 (60%)

The distribution of the drug combinations according to drug groups was also examined.In the single drug group, the percentage (52.4%) of drugs that did not include antidepressants was higher than the percentage of drugs that included only antidepressants (40%) and the percentage of the mixed group (0%).

In the combination of two drugs group, the percentage of drugs that included only antidepressants (60%) was higher than the percentage

of drugs that did not include antidepressants (33%) and the percentage of the mixed group (0%).

In the combination of three or more drugs group, the percentage of mixed type drugs (100%) was higher than the percentage of drugs that included only antidepressants (0%) and the percentage of drugs that did not include antidepressants (14.3%) (Table 3).

Table 3: Evaluation of Drug Combinations According to Drug Groups

Combination	Including Only Antidepressants N (%)	No Antidepressants N (%)	Mixed N (%)
Single Drug	2 (40%)	11 (52.4%)	0 (0%)
Two Drugs	3 (60%)	7 (33.3%)	0 (0%)
Three or More Drugs	0 (0%)	3 (14.3%)	5 (100%)

The distribution of time to death according to drug groups was investigated.

In the group of cases who died on the same day as the overdose, the percentage of "only antidepressants" (80.0%) was higher than the percentage of "no antidepressants" (47.6%) and the percentage of mixed type drugs (40%).

In the group of cases who died after intensive care treatment, the percentage of the mixed group (60%) was higher than the percentage of "only antidepressants" (52.4%) and the percentage of "no antidepressants" (20.0%).

Sixteen subjects were found dead at the scene of the overdose, while the remaining 15 subjects died in 3.64±4.70 days under intensive care treatment.

DISCUSSION

Methods of suicide vary between countries. Tsirigotis et al. have indicated that the most common method of suicide attempts was by taking pharmacological drugs (42.31%) and that this method was preferred by women (6). Chia et al. have reported that the most common method of suicide was jumping from high-rise buildings (72.4%) and that this method was preferred by younger females (7). In a study conducted in the emergency service, Çetin and colleagues evaluated 100 (1.7%) intoxication cases and found that 71% of the cases were females and the most common agent was medicinal products for human use (46%). Eighty-seven percent of the subjects received intensive care treatment and 13% were treated and followed up in the emergency ward; the mortality rate was 0% (8). Şenol et al. have reported that 63.0% of the sampled subjects were female and that the most common method of suicide was medicinal products for human use (65.5%) while the second most common method was jumping from high-rise places (16.5%). The same study reported that 1.8% of the attempts resulted in death and mortality was highest among who jumped from high-rise places (33.3%), 76% of the subjects were treated in emergency services and discharged with recovery, and that 22.2% of the subjects were hospitalized in intensive care units where the median duration of hospitalization was 2.5 days (min-max:1-45) (5). In our study, there were 4 females (57.1%) younger than 30 years of age and 9 older than 30 years of age (37.5%). Fifteen subjects died during intensive care treatment in 3.64±4.70 days.

A study conducted by Kekeç et al. has indicated that suicide was the intended purpose in 93.8% of the intoxication cases. In the same study, it was shown that the most common method (n=185; 47.6%) was to ingest two different pharmaceutical products at a time, while the least common way was taking nine different preparations (n=1; 0.3%) at a time. The majority of combinations of two drugs was analgesic-anti-inflammatory and antibiotic drugs (n=83; 23.8%) (9). Gündüz et al. conducted a study in emergency wards with intentional self-intoxication cases and showed that 69.7% of the subjects took drugs/substances prescribed for personal use while 30.4% of the subjects took drugs/substances prescribed for others; 53.1% of the subjects took a single drug while 46.9% took more than one drug. The most common type of drug was analgesics, followed by antidepressants and antipsychotics (10). In this study, all subjects who completed suicide had been diagnosed as suffering from major depression previously. In our study, we revealed that in the combination of two drugs group, there were three individuals (60%) that included only antidepressants and seven individuals in the group which did not include antidepressants

(33.3%). In this study 13 subjects committed suicide by taking a single drug and in only two of those individuals, antidepressants (amitriptyline and citalopram) and in another individual the antipsychotic drug quetiapine were the cause. A study published by Simon et al. resulted in increased emphasis on the U.S. Food and Drug Administration's (FDA) warning about increased suicidality with antidepressant treatment. Based on medical records, this study reported that, between 1992-2003, 40 out of 100,000 episodes with medical intervention resulted in death in the first 6 months after a prescription in 65,103 patients with 82,285 episodes of antidepressant treatment (11).

In their study, Turgut et al. have revealed that 54.8% of the subjects were intoxicated with a single agent among individuals who attempted suicide and had a drug intoxication. In the order of frequency, the agents were analgesics (33.4%), antidepressants (29.3%), cardiovascular drugs (11.7%), antibiotics (11%), and antiepileptics (10%). As can be seen, antidepressants are second in frequency. A study by Fuller et al. has indicated that 51.3% of the subjects took more than one drug (mean 2.4) (12). A study conducted in England has reported that the most commonly identified drugs taken in fatal overdose were products with paracetamol , benzodiazepines and tri/tetracyclic antidepressants (13). Consistent with this report, in our study, depression patients usually preferred drugs other than antidepressants for suicide. In our study, we determined that all subjects took the agent orally. Another study reported that 99.1% of the patients were intoxicated after intake through gastrointestinal route (14).

The study by Fuller et al. revealed that 33.3% of the subjects had high levels of alcohol (12). In our study, ethanol was found in only 2 subjects.

Thirteen (41.9%) females and 18 (58.1%) males were evaluated in our study. The study by Kekeç et al. was conducted with individuals who were intoxicated with multiple drugs where 68.5% of the subjects were female. It has been known that, in general, suicide attempts are more common among females while completed suicides are more common among males. In Turkey, at all ages, the male to female ratio of completed suicide to suicide attempt is 2 (2). In our study, we did not find a significant difference between males and females in terms of drug intoxication resulting in death. Therefore, it can be suggested that there are no differences in completed suicides by taking drugs between men and women, and that males complete suicide more commonly by using other methods of suicide which result in death more frequently than women.

Kekeç et al. found that three hundred and twenty-two subjects were between 15-34 years of age (82.8%) (9). In our study, completed suicide was most common among individuals between 31-40 years of age (11 subjects); the youngest subject was 16 years old and the oldest was 82 years old. Suicide was more common in the age group of ≥30 years.

Three hundred and thirty seven patients were under observation in the emergency service due to drug intoxication in the study by Kekeç et al.; 52 (13%) of these patients received intensive care treatment and none of the patients died (9). Taking a one to two-week dose of a tricyclic antidepressant at once may be more lethal than taking high doses of serotonin reuptake inhibitors. A study found that coma and intensive care unit admission were less likely in 233 individuals who attempted suicide by taking a serotonin reuptake inhibitor than 172 individuals who took tricyclics (for coma 17.7% vs 1.3%; for intensive care unit admission 45.9% vs 7.3%) (15). It is very probable that we would find lower blood antidepressant levels in subjects who died after emergency ward admission than those who took a lethal dose.

In our study we found that three subjects committed suicide by taking metformin only. Patients with diabetes must be closely monitored for depression. National and international studies have shown that individuals with diabetes are at increased risk for depression (16,17,18). In recent years, studies investigating the use of metformin to treat antipsychotic induced weight gain in individuals with schizophrenia are increasing (19). Another importance of this study is that it revealed the need to be on the alert in overweight depressive patients.

The drug we encountered most frequently in our study was quetiapine. However, quetiapine was

found more commonly as a part of drug combinations in completed suicides. Quetiapine was taken as a single agent only in one subject and in that subject the quetiapine dose was found to be lethal. Death due to overdose of quetiapine, a second generation antipsychotic, has not been reported in the scientific literature. There have been no studies which compared the lethality of antidepressants and second generation antipsychotics usedto treat depression. However, it has been suggested that acute overdose of second generation antipsychotics may be more lethal than overdose of first generation antipsychotics (20). It is not possible to formulate conclusions on the safety of quetiapine based on our study.

Fuller et al. found benzodiazepines in 35% of the sampled subjects (12). In our study, the two drugs that we frequently encountered in four subjects for each were amitriptyline and diazepam. However, as with quetiapine, we cannot make any negative comments on the safety of these two drugs since both were taken in combination with other drugs in high doses and combined with intensive care treatment.

CONCLUSION

Drugs that are observed to be more lethal and are used more frequently must be kept under control. When taking informed consent, patients must also be informed about the consequences of taking an overdose in the same way that they are informed on the effects of the drug at therapeutic doses. A history of depression must be questioned particularly for the individual taking the drug. Along with this issue, a history of depression must be questioned for other people living in the same house. Drugs must be given to depressive patients not as a whole box but in smaller dosage units (21). In conjunction with this preventive measure, the remainder of the medication must be stored in a place where access is restricted, when necessary.

When the health expenses of patients with major depression are reimbursed, the cost of safe storage of medications might also be covered by the social security agencies. Low-cost safe storage cases can be prescribed and can be distributed to caregivers, with informed consent.

Depressive patients on metformin must be closely evaluated and followed with particular vigilance.

Acknowledgement

We express our gratitude to Nihal Altıntepe from EMPIAR Statistics for her contribution to the statistical analysis.

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