DETOXIFICATION METHODS OF BENZODIAZEPINES MONO-DEPENDENCE: APPLICATION AND COMPARISON

BY

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ABSTRACT

Benzodiazepines are common drugs of abuse in Egypt and produce severe suffering during withdrawal which magnifies the need to develop treatment strategies for discontinuing these medications. The study aimed to evaluate different detoxification procedures that have been followed to manage benzodiazepines dependence and to assess their efficiency in controlling withdrawal symptoms and relapse rates. This study had been conducted in the center of Psychiatry, Neurology and Neurosurgery, Faculty of Medicine, Tanta University, Egypt. It lasted for 45 days and was divided into three phases; pretreatment phase (7 days), detoxification phase (8 days) and follow-up phase (30 days). Three different methods of detoxification of benzodiazepines dependence were applied during the detoxification phase and included 1) slow flumazenil infusion (1mg/500ml saline twice daily) as the main line of treatment with low doses of oxazepam given orally during the first three nights of detoxification phase 2) gradual tapering using oxazepam and 3) abrupt discontinuation of benzodiazepines with symptomatic treatment. Withdrawal symptoms were assessed by psychometric scales BWSQ, HAM-A, HAM-D scores and craving was assessed by VAS scores emerged in the three studied groups during the detoxification phase. The study revealed that flumazenil infusion with low doses of oxazepam was associated with the least intensity of withdrawal symptoms and craving. Also, relapse rates were decreased in patients treated with flumazenil than those treated by oxazepam tapering or abrupt discontinuation with symptomatic treatment. It can be concluded that slow flumazenil infusion with low doses of oxazepam appeared to be the most effective in controlling withdrawal symptoms, reducing craving and relapse rate after benzodiazepine discontinuation.

Keywords: *Benzodiazepines abuse, drug dependence, treatment of addiction, drugs of abuse detoxification, addiction, drug screening.*

INTRODUCTlON

Benzodiazepines are psychoactive drugs that increase the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA-A receptors, which produce sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant effects (Greenblatt et al., 1983). Benzodiazepine dependence produces both physical and psychological dependence and is associated with a withdrawal syndrome during dose reduction or stoppage. Recent guidelines recommend benzodiazepines to be used for short term periods, when strictly indicated and do not prefer their longer use because of their dangerous side effects (dependency, cognitive impairments, unwanted sedation, reduced coordination, falls, traffic accidents, etc.). In spite of the need for regular benzodiazepines use when indicated, the problem of benzodiazepines abuse and dependence appears in many patients (Lopez–Munoz et al., 2011 and Faccini et al., 2012). Management of benzodiazepine dependence involves not only short-term interventions such as detoxification but also psychological interventions and rehabilitation programs. Detoxification aims to get rid of the drug of dependency in a controlled and humane fashion and enhancement of treatment retention and detoxification success rates while reducing degree of discomfort. Although detoxification is viewed as an ineffective stand-alone treatment for drug dependence, it is a must for starting long-term abstinence-based treatments (Lader et al., 2009 and Veilleux et al., 2010).

Generally, detoxification can be achieved by one of the two approaches of detoxification: abrupt discontinuation of drug use or gradual tapering of the drug. Benzodiazepine dependence is usually treated with tapering of the medication or by substitution by an equivalent dose of a long half-life benzodiazepine drug before tapering, especially when patients are difficult to be treated or have low compliance to treatment. However there is no obvious evidence suggesting the optimum rate of tapering (Quaglio et al., 2005 and 2012).

Various adjunctive treatments have been advocated as effective medications in the treatment of benzodiazepine dependence. These drugs can be given to decrease the symptoms of withdrawal when they emerge. The best examples for these drugs are antidepressants and antipsychotics that have serotonin as well as dopamine-blocking actions. Carbamazepine has also some evidence supporting its use. A different approach of particular pharmacological interest as sudden cessation of the drug and a rapid benzodiazepine detoxification using flumazenil has been suggested (Hood et al., 2009 and Lader, 2011).

Flumazenil is a medication commonly used in the treatment of acute benzodiazepine toxicity. It is usually known as a benzodiazepine antagonist. Nonetheless, in chronic benzodiazepine users, it works as a partial agonist. Flumazenil has been shown to reduce the physical signs of benzodiazepines discontinuation and to reverse anxiety in benzodiazepines' dependent patients (Quaglio et al., 2005 and Lader, 2011).

The current study aimed to compare three different methods of detoxification of benzodiazepine dependence as regard disappearance of withdrawal syndrome and relapsing rate.

PATIENTS AND METHODS

Patients:

The present study was conducted on 45 Egyptian long-term benzodiazepines' dependent male patients seeking treatment for benzodiazepines' dependence at the center of Psychiatry, Neurology and Neurosurgery, Faculty of Medicine, Tanta University.

Inclusion criteria: 1) patients fulfilling the criteria for benzodiazepines' dependence according to criteria of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994). 2) patients whose benzodiazepines' dependence was reported as the main reason for seeking treatment. 3) patients dependent on benzodiazepines continuously and regularly for at least 2 years. Exclusion criteria: 1) patients with liver and/or kidney diseases or cardiac insufficiencies. 2) patients with history of urinary retention, narrow angle glaucoma or increased intraocular pressure. 3) patients with history of seizures or with concomitant psychiatric or neurological disorders. 4) patients dependent on alcohol and/or other drugs of abuse (opiates, tramadol, barbiturates, cocaine, cannabinoids and amphetamines). 5) patients receiving theophylline, carbamazepine, chloral hydrate, chloroquine, chlorinated hydrocarbons and tricyclic antidepressants.

The study was performed following approval of the medical research ethical committee of Tanta Faculty of Medicine. Each patient signed a written informed consent before starting the study and after complete and extensive description of the study. Their personal and medical data, observations, investigations and treatment data were recorded in special sheets. Privacy and confidentiality of patients' data and records were ascertained through coding system.

Materials :

Kits include alanine aminotransferase, aspartate aminotransferase and al-

kaline phosphatase (Biosystems S.A. Costa Brava 30, Barcelona, Spain), total and direct bilirubin and creatinine (Spectrum, Egyptian company for Biotechnology (S.A.E), Cairo, Egypt), total serum proteins (Futura system S.R.l. Roma, Italy), urea (Diamond Company, Hannover, Germany). Quick Profile™ DOA/Alcohol Panel Test Device (one step drug of abuse rapid test; Lumi Quick Diagnostic Inc., Santa Clora, CA, USA).

Drugs include Oxepam® (15 mg of oxazepam capsules; Alpha Chem. Advanced Pharmaceutical Industries Co., Badr city, third industrial zone, Cairo, Egypt), Seroquel® (100 mg of quetiapine fumarate tablets; Astra Zeneca group of companies, Egypt), Anexate® (0.5 mg of flumazenil in 5 ml aqueous solution ampoules; Roche made for F. Hoffman-La Roche Ltd, Basel, Switzerland by Cenexi SAS, Fontenay-sous-Bios, France), Tegretol® (200 mg carbamazepine tablets; Novartis Pharma S.A.E. Cairo, under license from Novartis Pharma AG, Basel, Switzerland), Tryptizol (25 mg of amitriptyline hydrochloride tablets; Kahira Pharm. & Chem. Ind. Co., Cairo, Egypt).

Study design :

The study lasted for 45 days and was divided into three phases; pretreatment phase, detoxification phase and follow-up phase (table 1). The studied patients were randomly classified into three equal groups (n=15/group) including group A: flumazenil group, group B: oxazepam tapering group and group C: abrupt oxazepam discontinuation with symptomatic treatment group.

1-Phase I (pretreatment phase- 7 days): The benzodiazepine dose taken by the patient was changed to the equivalent dose of oxazepam during the pretreatment phase according to the conversion table used to obtain a sample of patients homogenous for the type of a benzodiazepine drug before detoxification (Ashton, 2005). For group C: to avoid severe withdrawal manifestations before abrupt withdrawal of oxazepam the patients received 1) Seroquel®, an antipsychotic medicine (100 mg quetiapine fumarate tablets): 100 mg/day given orally at the nights of the first and second days, then given twice daily as follows: 200 mg/day on the third and fourth days and 300 mg/day on the fifth, sixth and seventh days of pretreatment phase (Sattar et al., 2004 and Erdogan, 2010). 2) Tryptizol, a tricyclic antidepressant (25 mg of amitriptyline hydrochloride tablets): given orally 50 mg/day given at the nights of the first and second days, then the dose was divided into two times daily doses and given as 100 mg/day on the third and fourth days, 125 mg/day on the fifth and sixth days and 150 mg/day on the seventh day

(Altinoprak et al., 2008).

2-Phase II (detoxification phase-8 days): Patients were subjected to treatment in the studied groups as follows. Group A patients were treated with slow intravenous flumazenil infusions for eight days and low doses of oxazepam according to the methods of Gerra et al., 2002 and Hood et al., 2009 (Table 2). Group B patients were treated by tapering of oxazepam over eight detoxification days to reduce benzodiazepine consumption to zero by the end of this time (Gerra et al., 2002). Group C patients received symptomatic treatment after abrupt discontinuation of oxazepam. It included: i) Seroquel® given orally, the dose was divided into two times daily: 300 mg/day on the first three days, 200 mg/day on the next three days, then 100 mg/day on the last two days of detoxification phase. ii) Tryptizol given orally, the dose was divided into two times daily doses: 150 mg/day on the first and second days, 100 mg/day on the third and fourth days, 75 mg/day on the fifth and sixth days and 50 mg/day on the seventh and eighth days (once at night) of detoxification phase. iii) Tegretol® (200 mg of carbamazepine tablets, anticonvulsant): 400 mg/day (one tablet twice/day) on the first and second days, 600 mg/day (one tablet three times/day) on the third and fourth days, 400 mg/day (one tablet twice /day) on the fifth and sixth days and finally 200 mg/day (one tablet/day) on the nights of the seventh and eighth days of detoxification phase (Ries et al., 1989 and DuPont, 1990).

3-Phase III (follow-up phase- 30 days): Relapse was determined by detecting benzodiazepines in urine after 15 and 30 days from the end of detoxification phase. Relapse is indicated by receiving a benzodiazepine drug during follow-up phase. For group C (Abrupt oxazepam discontinuation group) only, the patients were discharged on carbamazepine 200 mg/day (one tablet once at night) for two weeks (Ries et al., 1989).

For each patient the followings were obtained: socio-demographic data (age, special habits such as smoking, coffee and/or alcohol), patient's history of benzodiazepines use (name of the drug(s), route of intake, age of onset of intake, duration of intake, regularity of use, daily dose and motives for intake, drugs currently used and history of previous relapses), clinical evaluation (general examination, vital signs, systemic examination of head & neck, skin & extremities, chest & heart, gastrointestinal and neurological examination), psychiatric interviews and psychometric testing, investigations including laboratory investigations and electrocardiography (ECG).

Samples collection and preparation:

1) Urine samples: 20 ml urine samples

were obtained from each patient on admission, before starting detoxification phase; at the end of detoxification phase; 15 and 30 days after the end of detoxification phase for toxicological analysis. Samples were collected in clean dry sterile disposable containers (polypropylene), labeled with patient's name, serial number and date of sampling. If not analyzed immediately, specimens were stored at room temperature (15-25ºC) for up to seven days following collection. After seven days, specimens were stored frozen (-20ºC). Frozen specimens must be completely thawed and mixed thoroughly prior to analysis. Samples should be within the pH range 5-8. Add 1ml HCl or 1ml NaOH if adjustment of pH is necessary. Specimens with high turbidity should be centrifuged before analysis .

2) Blood samples: venous blood samples were obtained from each patient immediately on admission before oxazepam replacement's doses and after stoppage of treatment. Ten milliliters of venous blood were taken under complete aseptic conditions. Five milliliters were kept into a clean dry centrifuge tube and left to stand for few hours before centrifugation to avoid hemolysis. Serum was separated and then used to perform the biochemical analysis. The other five milliliters of venous blood were used for hematological analysis.

Biochemical analysis includes liver enzymes and liver function tests, kidney function tests and complete blood count.

Toxicological analysis

a. Rapid screening test (Quick Profile™ Drugs of Abuse/Alcohol Test Device).

It is an immunoassay based one step in vitro test, designed for qualitative determination of illicit substneces (benzodiazepines, opiates, tramadol, barbiturates, cocaine, cannabinoids, and amphetamines) and their metabolites in human urine specimens according to Liu and Goldberger (1995).

b. Viva-E analyzer (Drug Testing System, Siemens Healthcare Diagnostics Inc., Illinois, U.S.A). Previously mentioned kits were used for qualitative screening analysis of benzodiazepines, opiates, tramadol, barbiturates, cocaine, cannabinoids, and amphetamines in human urine. Syva® and Emit® II Plus benzodiazepine assay kits, Siemens Healthcare Diagnostics Inc., Newark, U.S.A. Kits were used for semi-quantitative analysis of benzodiazepines in human urine. Kits were automated using a Viva-E analyzer in Mabarrat-alasafra laboratories, Alexandria. The Cut off level for positive results is 200ng/ml.

Psychiatric assessments:

Diagnostic assessments were performed with the Structured Clinical Inter-

view for Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM–III–R): Patient Edition (SCID-P) (Spitzer and Williams, 1985) and the Structured Clinical Interview for DSM–III–R Personality disorders (SCID-II) (Spitzer et al., 1990). All of the patients were diagnosed as benzodiazepines' dependence.

Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ):

The primary outcome criterion was the extent of withdrawal symptoms assessed with Tyrer BWSQ (Tyrer et al., 1990). This scale evaluates twenty clinical signs of withdrawal, each scored between 0 and 2 (0 = absence of symptoms; 1 = moderate symptoms; 2 = severe symptoms). The total score thus obtained ranged from 0 to 40. Questions were related to symptoms such as feeling unreal, very sensitive to noise, light, smell and touch, peculiar taste in mouth, pain and twitching in muscles, dizziness and loss of appetite. BWSQ was applied at the end of pre-treatment phase (base line) and at the end of each day of the detoxification phase.

Visual Analogue Scale (VAS):

The VAS has been frequently used to quantify craving for drugs and has been used as a subjective measure of benzodiazepines' craving (McCormack et al., 1988). It can be completed in two minutes. The VAS consisted of a 100 mm horizontal line anchored on the left with 0 (no craving) and on the right with 100 (most craving ever felt for benzodiazepine). Visual analogue scale measured at the end of pre-treatment phase (base line) and at the end of each day of the detoxification phase.

Hamilton Anxiety Rating Scale (HAM-A):

This scale was used to assess the severity of anxiety during the withdrawal period. This scale evaluates fourteen items. Items are scored from 0 to 4 (0 - absent; 1 - mild; 2 - moderate; 3 - severe; 4 – incapacitating), the higher the score, the more severe the anxiety (less than 17 =mild, 18-24= moderate and 25-30= moderate to severe). Questions are related to symptoms such as anxious mood, tension, fears, insomnia, difficulties in concentration and memory, and autonomic symptoms (Hamilton, 1959). Hamilton Anxiety Rating Scale was measured at the end of pre-treatment phase (base line) and at the end of each day of the detoxification phase.

Hamilton Depression Rating Scale (HAM-D)

This scale was used to assess the severity of depression during the withdrawal period. It evaluates twenty one-item. Items are scored from 0 to 4 (0 - absent; 1 - mild; 2 - moderate; 3 - severe; 4 – incapacitating), the higher the score, the

more severe the depression. Hamilton Depression Rating total score is 10-13 for mild depression; 14-17 for mild to moderate and > 17 for moderate to severe depression. Questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels and weight loss (Hamilton, 1960). Hamilton Depression Rating Scale was measured at the end of pre-treatment phase (base line) and at the end of each day of the detoxification phase.

Statistics:

Statistical presentation of the present study was conducted using the mean and standard deviation. Analysis of variance [ANOVA] and Student t-tests were used. Pearson correlations coefficient were done between scores of different psychometric scales and ages, age of onset, dose and duration of benzodiazepine intake of the studied patients. Tukey's post hoc tests were used to make a quick comparison of several groups that have different numbers. All were done using SPSS (Statistical Package for the Social Science) version 17 computer program, Chicago, USA. The level of statistical significance was set at p-value below 0.05.

Table (1) : Phases of management of the studied benzodiazepine dependent patients (n=45).

Groups	Pretreatment phase (7 days)	Detoxification phase (8 days)	Follow-up phase (30 days)
Group A	Oxazepam	Flumazenil (8 days) + Oxazepam (3 days)	Benzodiazepine free
Group B	Oxazepam	Oxazepam tapering	
Group C	Oxazepam + Quetiapine (100 mg) + Amitriptyline (25 mg)	Symptomatic treatment	

Table (2) : Treatment schedule of group A (Flumazenil group; n=15) during detoxification phase (8 days) (Gerra et al., 2002 and Hood et al. 2009).

Days	Flumazenil	Oxazepam
Day 1	1mg flumazenil in 500ml saline IV infusion from 9am to 1pm 1mg flumazenil in 500ml saline IV infusion from 2.30 to 6.30pm	30mg, orally at 7.30 pm 30mg, orally at 11.30pm
Day 2	1mg flumazenil in 500ml saline IV infusion from 9am to 1pm 1mg flumazenil in 500ml saline IV infusion from 2.30 to 6.30pm	15mg, orally at 7.30 pm 15mg, orally at 11.30pm
Day 3	1mg flumazenil in 500ml saline IV infusion from 9am to 1pm 1mg flumazenil in 500ml saline IV infusion from 2.30 to 6.30pm	15mg, orally at 11.30pm
Day 4	1mg flumazenil in 500ml saline IV infusion from 9am to 1pm 1mg flumazenil in 500ml saline IV infusion from 2.30 to 6.30pm	No oxazepam
Day 5	1mg flumazenil in 500ml saline IV infusion from 9am to 1pm 1mg flumazenil in 500ml saline IV infusion from 2.30 to 6.30pm	No oxazepam
Day 6	1mg flumazenil in 500ml saline IV infusion from 9am to 1pm 1mg flumazenil in 500ml saline IV infusion from 2.30 to 6.30pm	No oxazepam
Day 7	1mg flumazenil in 500ml saline IV infusion from 9am to 1pm 1mg flumazenil in 500ml saline IV infusion from 2.30 to 6.30pm	No oxazepam
Day 8	1mg flumazenil in 500ml saline IV infusion from 9am to 1pm 1mg flumazenil in 500ml saline IV infusion from 2.30 to 6.30pm	No oxazepam

RESULTS

Socio-demographic data :

The ages of the patients ranged from 22 to 60 years old with mean ages 36.93 ± 8.21, 38.33 ± 9.74 and 38.4 ± 8.36 years in groups A, B and C respectively with no significant differences ($p > 0.05$).The current study showed that all patients were current cigarette smokers whereas the majority of patients were caffeine users (86.67%, 93.33% and 86.67% in groups A, B and C respectively).

History of benzodiazepines abuse:

All patients were taking a benzodiazepine drug orally in the form of tablets. Clonazepam was used among 53.33%, 60.00% and 46.67% of the studied patients in group A, B and C respectively. Alprazolam was used among 26.67%, 26.67% and 33.33% of patients in groups A, B and C respectively. Lorazepam was used among 20.00%, 13.33% and 20.00% of the studied patients in the studied groups respectively. There was no significant difference between the three studied groups (A, B and C) as regards ages of onset of benzodiazepine intake ($p > 0.05$). Mean ages of onset of intake were 33.47 ± 7.43, 34.87 ± 9.01 and 34.80 ± 7.31 years in groups A, B and C respectively. Duration of benzodiazepine intake in the studied patients ranged from 2 to 7 years with mean duration 3.47 ± 1.06, 3.33 ± 1.05 and 3.6 ± 1.45 years in groups A, B and C respectively. No significant difference was found between the three studied groups ($p > 0.05$). The studied patients were switched to equivalent doses of oxazepam. Doses varied from 80 to 480 mg/d. The mean equivalent doses of oxazepam were 258.67 ± 103.50, 306.67 ± 87.72 and 301.33 ± 94.25 mg/d in the studied groups (A, B and C respectively) with no significant differences between the studied groups ($p > 0.05$).

Psychometric scales :

Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire (BWSQ): there was no significant change in the mean BWSQ scores in the base line between the three studied groups (6.93 ± 1.22, 7.13 ± 1.13 and 7.07 ± 1.22 for groups A, B and C respectively, $p > 0.05$). As well, group A showed no significant change ($p > 0.05$) in the mean BWSQ scores on the first, second and third days of detoxification phase as compared with group C, but it showed time dependent significant change from the fourth day to the end of detoxification phase as compared with group C (abrupt oxazepam discontinuation group) ($p < 0.05$) (Figure 1).

Hamilton Anxiety Rating Scale (HAM-A). Group A showed no significant change in the values of HAM-A scores from the first to the fifth day of detoxification as

compared with group C (abrupt oxazepam discontinuation group) ($p > 0.05$), but it showed significant change in their values on the last three days of detoxification phase when compared with group C ($p < 0.05$) (Figure 2).

Hamilton Depression Rating Scale (HAM-D). There was time dependent significant changes from the first day to the last day of the detoxification phase in group A as compared with group B and in group B compared with group C . However, group A showed no significant change in the values of HAM-D scores on the first, second and third days of detoxification as compared with group B ($p > 0.05$), but it showed significant change in their values with the time from the fourth day to the end of detoxification phase when compared with group B ($p < 0.05$) (Figure 3).

Visual Analogue Scale (VAS) :

There were significant changes in the mean Visual Analogue Scale (VAS) scores in group A as compared with group B from the second day to the last day of detoxification. Also, group A showed significant change on the last three days of detoxification phase when compared with group C ($p < 0.05$). Group B showed significant change in their values from the fifth day to the end of detoxification phase when compared with group C ($p < 0.05$) (Figure 4).

Systolic blood pressure:

The mean systolic blood pressure values in group A and in group C showed significant increase from the first day to the fourth day of detoxification then they showed significant decrease from the fifth day to the end of detoxification phase. While in group B the mean systolic blood pressure values were significantly increased from the first day to the sixth day of detoxification then they were significantly decreased on the last two days of detoxification phase ($p < 0.05$). There were significant changes in the mean systolic blood pressure values in group A as compared with group B and in group B as compared with group C from the fourth day to the end of detoxification phase ($p < 0.05$) (Figure 5).

Heart rate:

There were no significant changes between the three studied groups (A, B and C) in the mean heart rates of the patients on the first, second, third and fourth days of detoxification phase ($p > 0.05$). However, it showed time dependent significant changes between the three studied groups in the mean heart rates of the patients from the fifth day to the last day of detoxification phase ($p < 0.05$) (Figure 6).

Correlation between intensity of withdrawal symptoms assessed by different psychometric scales' scores and age, age of onset, dose and duration of benzodiaz-

epine intake:

At the end of detoxification phase of both groups B and C, there were significant correlations ($p < 0.05$) between the ages of the studied patients, age of onset, dose and duration of benzodiazepine intake and scores of all psychometric scales (BWSQ, HAM-A, HAM-D and VAS) as demonstrated in tables 3 and 4. No other significant correlations were found between the studied groups.

Toxicological and biochemical parameters of the studied groups:

At the beginning of the study and before starting detoxification, urine screening tests showed that, all patients enrolled in the present study were positive to benzodiazepines and negative to other drugs of abuse (opiates, tramadol, barbiturates, cocaine, cannabinoids and amphetamines). While, at the end of detoxification phase, urine screening tests showed that, all studied patients were negative to benzodiazepine. Benzodiazepine level was determined at the end of detoxification phase. In the present study, liver enzymes, liver function tests, kidney function tests and complete blood count of the studied patients after stoppage of treatment showed no significant changes between the three studied groups as compared with baseline values. They were within the normal range at the start and end of the study.

Outcomes (relapse rate)

After 15 days from the end of detoxification phase relapse rates were 33.33%, 60% and 40% in groups A, B and C respectively; while, they were 53.33%, 80% and 66.67% respectively after 30 days from the end of detoxification phase. There were no significant changes between the three studied groups (A, B and C) in the mean ages, age of onset, dose and duration of benzodiazepines intake of the relapsed patients ($p > 0.05$). However, the mean scores of psychometric scales (BWSQ, HAM-A, HAM-D and VAS) of the relapsed patients showed significant changes ($p < 0.05$) between the three studied groups (A, B and C) (Tables 5 and 6).

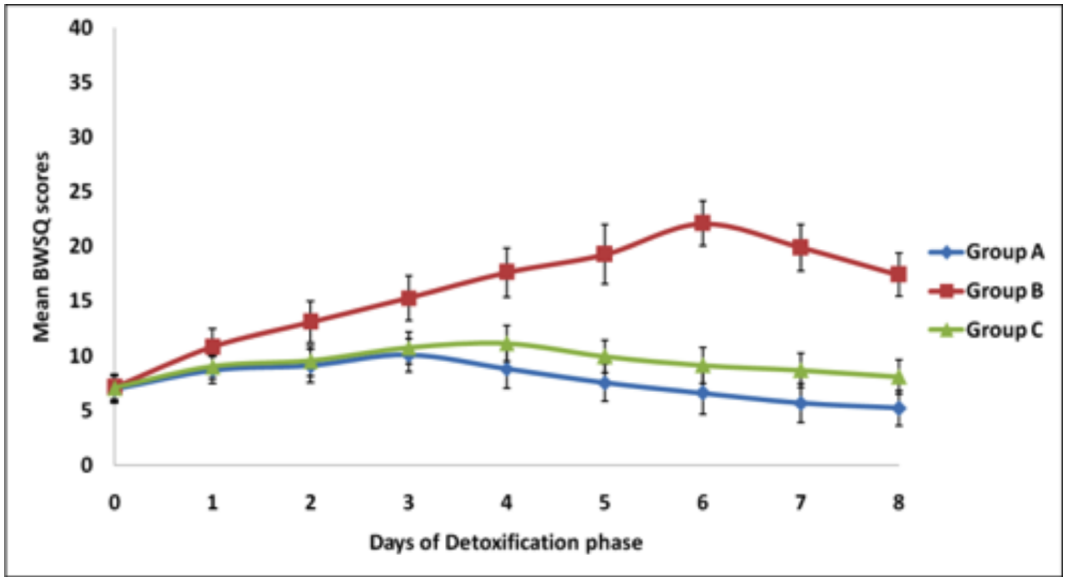

Fig. (1) : Mean scores of Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) in the studied groups of benzodiazepine dependent patients (n=45) during the detoxification phase (8 days) Group A: flumazenil group; Group B: oxazepam tapering group; Group C: abrupt oxazepam discontinuation group.

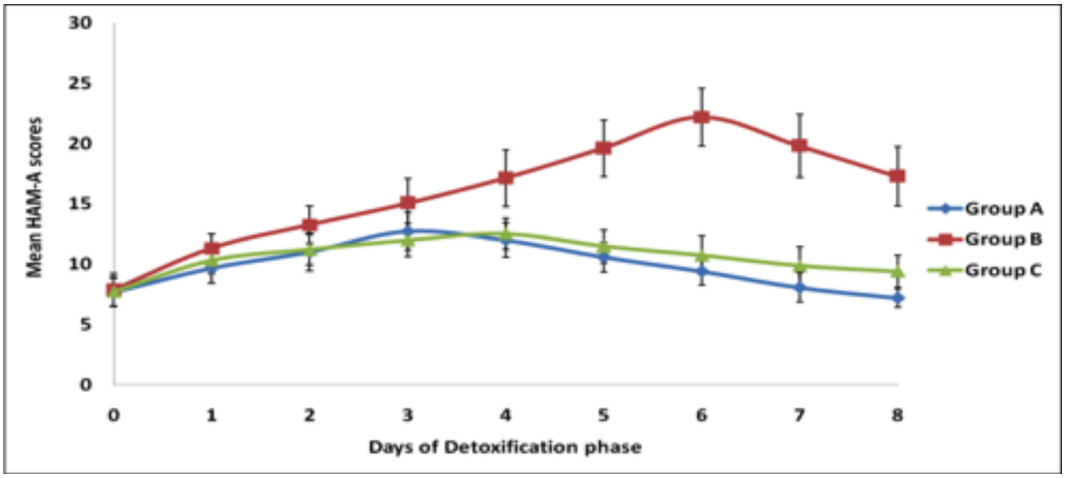

Fig. (2) : Mean scores of Hamilton Anxiety Rating Scale (HAM-A) in the studied groups of benzodiazepine dependent patients (n=45) during the detoxification phase (8 days). Group A: flumazenil group; Group B: oxazepam tapering group; Group C: abrupt oxazepam discontinuation group.

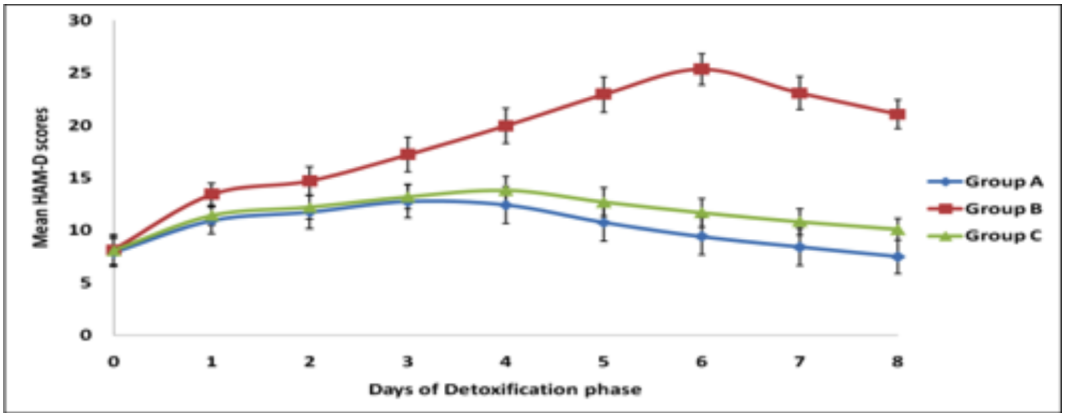

Fig. (3) : Mean scores of Hamilton Depression Rating Scale (HAM-D) in the studied groups of benzodiazepine dependent patients (n=45) during the detoxification phase (8 days). Group A: flumazenil group; Group B: oxazepam tapering group; Group C: abrupt oxazepam discontinuation group.

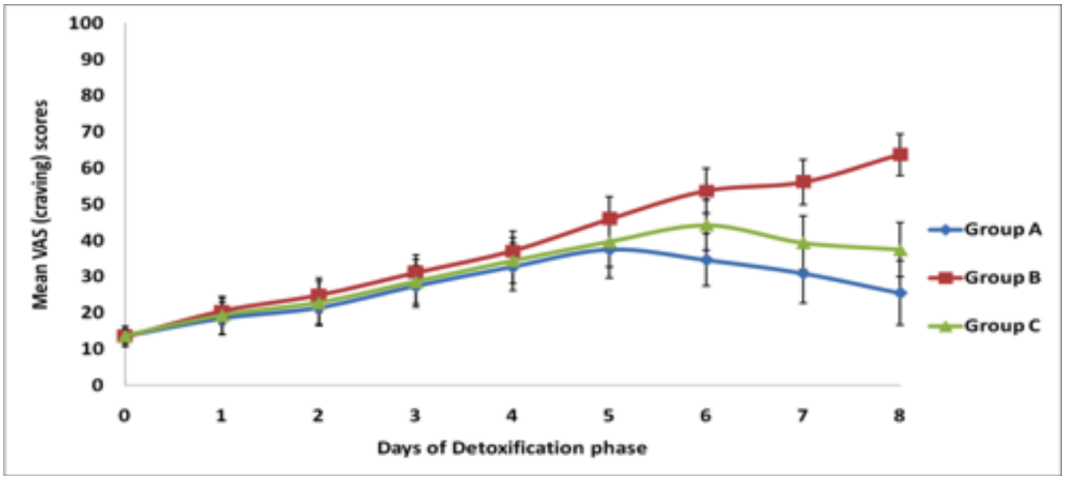

Fig. (4) : Mean scores of Visual Analogue Scale (VAS) in the studied groups of benzodiazepine dependent patients (n=45) during the detoxification phase (8 days) Group. A: flumazenil group; Group B: oxazepam tapering group; Group C: abrupt oxazepam discontinuation group.

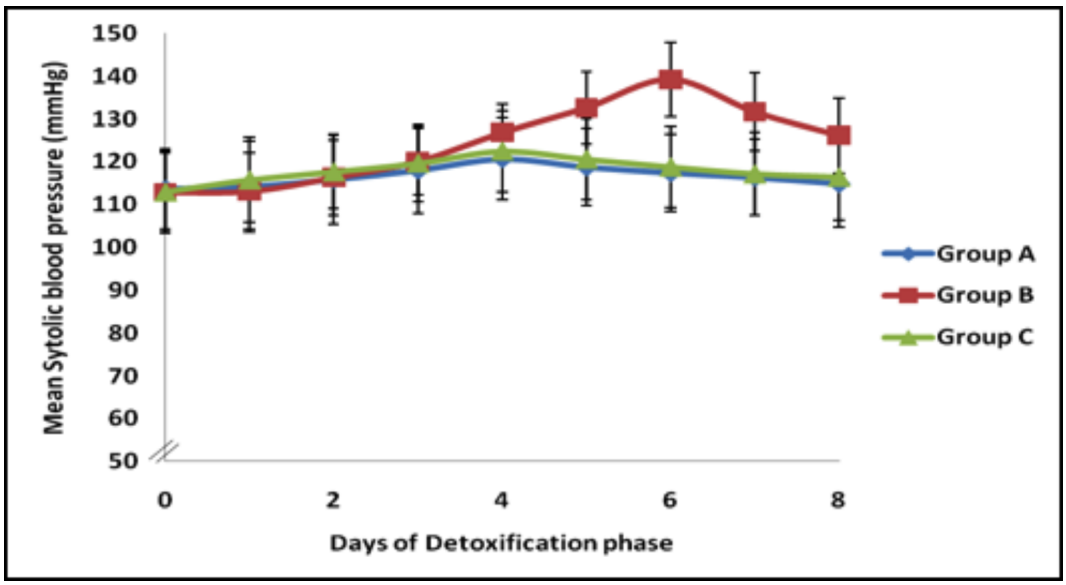

Fig. (5) : Mean systolic blood pressure (SBP) values in the studied groups of benzodiazepine dependent patients (n=45) during the detoxification phase (8 days). Group A: flumazenil group; Group B: oxazepam tapering group; Group C: abrupt oxazepam discontinuation group.

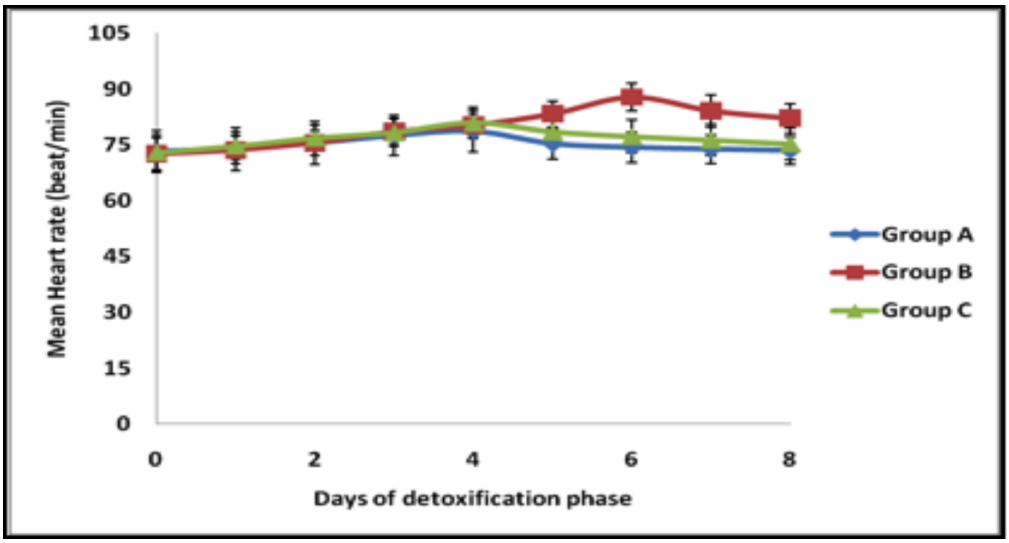

Fig. (6) : Mean heart rates in the studied groups of benzodiazepine dependent patients (n=45) during the detoxification phase (8 days). Group A: flumazenil group; Group B: oxazepam tapering group; Group C: abrupt oxazepam discontinuation group.

Table (3) : Pearson correlation coefficients between scores of different psychometric scales and age, age of onset, dose and duration of benzodiazepine intake group B at the end of the detoxification phase (8 days):

		BWSQ	HAM-A	HAM-D	VAS
Age	r	0.920**	0.946**	0.908**	0.930**
	p-value	0.000	0.000	0.000	0.000
Age of onset of BZ intake	r	0.991**	0.935**	0.898**	0.889**
	p-value	0.000	0.000	0.000	0.000
BZ dose	r	0.817**	0.798**	0.806	0.785**
	p-value	0.000	0.000	0.000	0.001
Duration of BZ intake	r	0.651**	0.656**	0.623*	0.567*
	p-value	0.009	0.008	0.013	0.028

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is highly significant at the 0.01 level (2-tailed). BWSQ: Benzodiazepine Withdrawal Symptom Questionnaire. HAM-A: Hamilton Anxiety Rating Scale. HAM-D: Hamilton Depression Rating Scale. VAS: Visual Analogue Scale.BZ: Benzodiazepine.

Table (4) : Pearson correlation coefficients between scores of different psychometric scales and age, age of onset, dose and duration of benzodiazepine intake in group C at the end of the detoxification phase:

		BWSQ	HAM-A	HAM-D	VAS
Age	r	0.841**	0.938**	0.898**	0.907**
	p-value	0.000	0.000	0.000	0.000
Age of onset of BZ intake	r	0.824**	0.933**	0.834**	0.874**
	p-value	0.000	0.000	0.000	0.000
BZ dose	r	0.834**	0.578*	0.659**	0.728**
	p-value	0.000	0.024	0.007	0.002
Duration of BZ intake	r	0.665**	0.559*	0.590*	0.612*
	p-value	0.007	0.030	0.021	0.015

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is highly significant at the 0.01 level (2-tailed). BWSQ: Benzodiazepine Withdrawal Symptom Questionnaire. HAM-A: Hamilton Anxiety Rating Scale. HAM-D: Hamilton Depression Rating Scale. VAS: Visual Analogue Scale.BZ: Benzodiazepine.

Table (5) : Pearson correlation coefficients between scores of different psychometric scales and age, age of onset, dose and duration of benzodiazepine intake in the relapsed patients (n=12) of group B (oxazepam tapering group; n=15):

		BWSQ	**HAM-A**	**HAM-D**	**VAS**
Age	r	0.915**	0.939**	0.876**	0.885**
	p-value	0.000	0.000	0.000	0.000
Age of onset of BZ intake	r	0.889**	0.922**	0.857**	0.835**
	p-value	0.000	0.000	0.000	0.001
BZ dose	r	0.733**	0.729**	0.717**	0.687*
	p-value	0.007	0.007	0.009	0.014
Duration of BZ intake	r	0.924**	0.897**	0.841**	0.914**
	p-value	0.000	0.000	0.001	0.000

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is highly significant at the 0.01 level (2-tailed). BWSQ: Benzodiazepine Withdrawal Symptom Questionnaire. HAM-A: Hamilton Anxiety Rating Scale. HAM-D: Hamilton Depression Rating Scale. VAS: Visual Analogue Scale. BZ: Benzodiazepine.

Table (6) : Pearson correlation coefficients between scores of different psychometric scales and age, age of onset, dose and duration of benzodiazepine intake in the relapsed patients (n=10) of group C (abrupt oxazepam discontinuation group; n=15):

		BWSQ	**HAM-A**	**HAM-D**	**VAS**
Age	r	0.854**	0.951**	0.926**	0.842**
	p-value	0.002	0.000	0.000	0.002
Age of onset of BZ intake	r	0.847**	0.951**	0.933**	0.839**
	p-value	0.002	0.000	0.000	0.002
BZ dose	r	0.967**	0.905**	0.892**	0.799**
	p-value	0.000	0.000	0.001	0.006
Duration of BZ intake	r	0.791**	0.845**	0.792**	0.764*
	p-value	0.006	0.002	0.006	0.010

* Correlation is significant at the 0.05 level (2-tailed).** Correlation is highly significant at the 0.01 level (2-tailed).BWSQ: Benzodiazepine Withdrawal Symptom Questionnaire. HAM-A: Hamilton Anxiety Rating Scale. HAM-D: Hamilton Depression Rating Scale.
VAS: Visual Analogue Scale.BZ: Benzodiazepine.

DISCUSSION

In the present study, all benzodiazepines' dependent patients with various benzodiazepines drugs were shifted to equivalent doses of oxazepam. The choice of oxazepam as alternative to all other benzodiazepines could be explained by its availability in Egypt and on the basis that the half-life of oxazepam is 5–15 hours. It is the most slowly absorbed benzodiazepine and has a slow onset of action. Therefore, oxazepam has a relatively low susceptibility for abuse compared to some other benzodiazepines (Serfaty and Masterton, 1993 and Lader, 2011).

In the current study, the equivalent doses of oxazepam in the studied patients varied from 80 to 480 mg/day. The mean equivalent doses of oxazepam were 258.67 ± 103.50, 306.67 ± 87.72 and 301.33 ± 94.25 in groups A, B and C respectively, reflecting the high doses of benzodiazepine used by the studied patients. Previous studies showed that the received doses of benzodiazepine drugs in dependent patients exceeded the therapeutic doses (≤ 30 mg diazepam per day) (Saxon et al., 1997; Gerra et al., 2002; Hood et al., 2009 and Quagilo et al., 2012). However, other studies demonstrated the use of therapeutic doses of benzodiazepines by chronic benzodiazepine dependents (Mintzer et al., 1999; Upadhayaya, 2000; Ribeiro et al., 2007 and Ahmer et al., 2009) which indicates that, benzodiazepines' dependence and withdrawal symptoms can occur not only from high doses but also from regular therapeutic doses of benzodiazepines (Ashton, 2005 and Lader et al., 2009).

In some cases, withdrawal syndrome may be severe enough to motivate the development of treatment strategies for discontinuing these medications. The common management of benzodiazepine dependence involves either gradual tapering of the drug or sudden cessation with switching to a longer half-life benzodiazepine or adjunctive medications (Denis et al., 2006; Voshaar et al., 2006 and Hood et al., 2009). Initially, flumazenil was considered as a 'pure' antagonist, later on subsequent work in both animals and humans has shown that flumazenil is a mixed agonist/antagonist, partly dose dependent (Thomson et al., 2006 and Lader et al., 2009).

In the present study, analysis of mean scores of BWSQ in group A (flumazenil group) revealed significant increase in these values from the first day to the third day of detoxification then they significantly decreased to the end of detoxification phase. In addition, analysis of mean HAM-A rating scale and HAM-D rating scale scores supported the results of BWSQ. Similarly, the mean VAS scores showed significant increase in their values from the first day to the fifth day of detox-

ification then they showed significant decrease on the last three days of detoxification phase.

For cardiovascular changes, the mean values of systolic blood pressure and heart rates showed significant increase in their values from the first day to the fourth day of detoxification then they significantly decreased from the fifth day to the end of detoxification phase. This agrees with the results of other studies which reported that flumazenil infusion was effective in reducing withdrawal syndrome in benzodiazepine dependent patients and was capable to reduce anxiety level and craving during detoxification period as well as inhibited the cardiovascular changes associated with the withdrawal syndrome (Gerra et al., 1993; Saxon et al., 1997; Gerra et al., 2002; Hood et al., 2009 and Lugoboni et al., 2011).

Flumazenil's effects may be due to tolerance reversal and attenuation of withdrawal symptoms, anxiety and craving mediated by normalization and up-regulation of benzodiazepine receptors facilitating coupling of the GABA-A receptors and benzodiazepines receptors complexes (Lader and Morton, 1992 and Quaglio et al., 2012). Also flumazenil can reset the benzodiazepine receptor set point that is shifted in the inverse agonist direction by chronic use of benzodiazepines and to increase receptor sensitivity which allows flumazenil to exert its weak partial agonist activity with possible enhanced efficacy. Finally, the capability of flumazenil to attenuate the urge to take benzodiazepines can be explained by its partial agonist activity (Quaglio et al., 2005; Jazvinscak, et al., 2008 and Quaglio et al., 2012). Similarly, the effectiveness of low-dose oxazepam administered in group A patients together with flumazenil, on the first three nights during the detoxification phase, could have been enhanced by receptor up-regulation (Lader and Morton, 1992 and Gerra, et al., 2002).

In the present study, the choice to use flumazenil twice a day in low doses with slow infusion rate was suggested due to the short half-life of the drug and previous effective experience in other studies. Also, this infusion level reach a small number of receptors which is consistent with the gradual improvement that occurs as long as the infusion is administered (Gerra et al., 1993; Gerra et al., 2002 and Quaglio et al., 2012). On the other hand, it was reported that bolus infusion of flumazenil (1 mg in 5 min) precipitated benzodiazepine withdrawal symptoms and was a powerful anxiety-provoking challenge (Mintzer et al., 1999 and Mintzer and Griffiths, 2005) but in the procedure utilized by these authors, flumazenil was injected in a short time (5 minutes). Furthermore, the subjects have been exposed to low doses of diazepam, which

might be related to lower tolerance levels (Gerra et al., 2002). It was reported that panic attacks had been developed in benzodiazepines dependent patients treated with flumazenil. Those patients have been observed that they had been diagnosed previously as having panic disorders, suggesting that flumazenil may not be responsible for provoking panic symptoms (Bernik et al., 1998 and Bell et al., 2002). Benzodiazepine tapering is a procedure used widely for its continuation. However, the rate of tapering is not supported by good empirical evidence but by the clinical experience of the author (Lader, 2011).

In group B, means BWSQ scores were significantly increased from the first day to the sixth day of detoxification then significantly decreased on the last two days of detoxification phase. Similarly, analysis of the mean values of HAM-A rating scale scores, HAM-D rating scale scores, systolic blood pressures and heart rates coincided with the results of BWSQ scores. While, the mean VAS scores showed significant increase from the first day to the last day of detoxification phase. The former data coincides with the results found by Gerra et al, (2002) who showed that in benzodiazepines' dependent patients treated by oxazepam tapering over eight days of detoxification, the patients reported increased withdrawal symptoms from the first day of detoxification, increased anxiety level, high craving scores and significant increase in the values of heart rate and systolic blood pressure from day 4 to day 8 during the eight days of detoxification procedure. These findings were attributed to increased distress and discomfort related to withdrawal symptoms with tapering of the benzodiazepine dose. In addition, high craving scores during the last days of oxazepam tapering were explained by persistent exposure to benzodiazepine, which may be responsible for priming compulsive behavior, with a trigger mechanism that increases craving levels for benzodiazepines (Self, 1998 and Gerra et al., 2002).

Group C (abrupt oxazepam discontinuation group) demonstrated significant elevation in the values of Tyrer BWSQ scores from the first day to the fourth day of detoxification then they significantly decreased from the fifth day to the end of the detoxification phase. Similar findings were demonstrated after analysis of mean HAM-A rating scale scores, HAM-D rating scale scores, systolic blood pressures and heart rates, while, the mean VAS scores showed significant increase from the first day to the sixth day of detoxification then decreased on the last two days of detoxification phase. These results could be attributed to the effect of antidepressant, antipsychotic and anticonvulsant effects which acted as prophylactic treatments for most commonly reported

withdrawal symptoms during detoxification phase. Various supportive treatments have been used for treatment of benzodiazepine withdrawal symptoms. These agents should help to attenuate the symptoms of withdrawal if they emerge. These drugs can be given as a prophylaxis or as needed. Some of these adjunctive agents were not helpful; however, others were effective, for example antidepressants and antipsychotics which have 5-HT blocking effects as well as dopamine-blocking actions have been reported as effective. Also, carbamazepine has some evidence supporting its use (Schweizer et al., 1991; Bourin et al., 2004; Lemoine et al., 2006 and Lader, 2011).

To the best of authors' knowledge, no previous study demonstrated the relation between the intensity of withdrawal symptoms after detoxification by different regimens and some factors like age, duration of benzodiazepine intake, the dose and age of onset of intake. The present study revealed that, in flumazenil treated patients, age of the patients, duration of benzodiazepine intake, dose and age of onset did not affect the intensity of withdrawal symptoms. While in patients treated with either oxazepam tapering or abrupt discontinuation, the intensity of withdrawal symptoms correlated significantly with these factors. Hence, it is recommended that age of patient, age of onset, dose and duration of benzodiazepines' dependence should be considered while choosing the regimen of choice for detoxification.

This study revealed that the relapse rates after 15 days from the end of detoxification phase were 33.33%, 60% and 40% in groups A, B and C respectively; while, they were 53.33%, 80% and 66.67% after 30 days from the end of detoxification phase. These results were near to those reported by Gerra et al. (2002) at day 15, day 23 and day 30 after detoxification in the studied benzodiazepine dependent patients treated with flumazenil infusion (25%, 30% and 40% respectively). While they were 55%, 60% and 70% at day 15, 23 and 30 after detoxification in benzodiazepine dependent patients treated with oxazepam tapering over the eight days of detoxification period. Flumazenil action on reducing subjective distress and craving after benzodiazepine discontinuation possibly due to increased benzodiazepine receptor sensitivity to endogenous ligands that may have helped to reduce to some extent the relapse rates in flumazenil treated patients (Saxon et al. 1997 and Vale et al., 1998). The high relapse rates found in benzodiazepines' dependent patients treated with oxazepam tapering could be attributed to high craving scores especially on the last days of detoxification phase and more consistent withdrawal symptoms (Gerra et al., 2002). This coincides with the observation of

other studies that early stages of withdrawal are more tolerable than the later and final stages (Michelini et al., 1996; Curran et al., 2003 and Lader, 2011). The relapse rates in group C patients treated with antidepressant, antipsychotic and anticonvulsant drugs, were less than that for patients of group B and slightly higher than that for patients of group A. This could be attributed to the ability of the treatment given to patients of group C to manage withdrawal symptoms during detoxification phase but not to relieve of craving or withdrawal symptoms after detoxification which was associated with increased relapse rate in the follow-up period.

Finally, as the main reasons for benzodiazepines intake tend to be chronic conditions (anxiety and insomnia), patients withdrawing from these drugs are liable to relapse. The observed relapse rates in patients treated from benzodiazepines' dependence are high and may be attributed to the fact that despite detoxification is a must for beginning long-term abstinence-based treatments, it is not considered a complete treatment for benzodiazepine dependence. An essential strategy for treatment has to be followed by psychological interventions and rehabilitation programs to continue the treatment successfully and maintain discontinuation (Lader et al., 2009 and Veilleux et al., 2010).

CONCLUSION

Flumazenil infusion with low doses of oxazepam appeared to be more effective in controlling withdrawal symptoms after benzodiazepine discontinuation with less incidence of relapse than oxazepam tapering or abrupt oxazepam discontinuation with symptomatic treatment. On the other hand, oxazepam tapering over eight days proved to be the worst of the detoxification methods regarding severity of withdrawal and incidence of relapse.

Limitations of the study:

It was conducted without double blinding, limited sample size and short follow-up period.

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طرق التخلص من السموم من الجسم في حالة الإدمان المنفرد للبنزوديازيبينز: تطبيق و مقارنة

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البنزوديازيبينز هي من أكثر الأدوية المخدرة انتشارا في مصر وقد أدت المعاناة الشديدة التي تحدث أثناء التوقف عن تعاطي البنزوديازيبينز بعد فترة إدمان طويلة إلى محاولة الوصول إلى إستراتيجيات مختلفة للتوقف عن تعاطي البنزوديازيبينز. وهدفت هذه الدراسة إلى مقارنة بين الطرق المختلفة المتبعة للتخلص من البنزوديازيبينز من الجسم ومدى كفاءتها في التحكم في أعراض الانسحاب. وقد أجريت الدراسة في مركز النفسية والعصبية وجراحة الأعصاب بكلية الطب ، جامعة طنطا، مصر. استغرقت الدراسة ٤٥ يوما وقسمت إلى ثلاث مراحل و تشمل هذه المراحل: مرحلة ما قبل العلاج و استغرقت ٧ أيام ثم مرحلة إزالة السموم و كانت لمدة ٨ أيام وأخيرا مرحلة المتابعة لمدة ٣٠يوما. تم تطبيق ثلاثة طرق مختلفة للتخلص من السموم من الجسم في حالة إدمان تعاطي البنزوديازيبينز وتضمنت الطريقة الأولى على التنقيط الوريدي البطيء لعقار الفلومازينيل بجرعة ١مجم/ ٥٠٠مللتر محلول ملحي مرتين يوميا كعلاج أساسي بالإضافة إلى جرعات منخفضة من عقار الاوكسازيبام عن طريق الفم أثناء الثلاث ليالى الأولى من العلاج. أما الطريقة الثانية فكانت بإستخدام الأوكسازيبام وتقليله تدريجيا حتى التوقف. وأما الطريقة الثالثة فشملت التوقف الفجائى للبنزوديازيبينز مع العلاج العرضي لإعراض الانسحاب. وقد قيمت أعراض الانسحاب بقياسات تنقيط نفسية و شملت **BWSQ, HAM-A, HAM-D** وتم قياس مدى الرغبة في العودة إلى التعاطي بنظام التنقيط **VAS** وذلك أثناء مرحلة إزالة السموم في الثلاث طرق المتبعة. و قد أسفرت الدراسة عن إن استخدام الطريقة الأولى و التي تضمنت استخدام عقار الفلومازينيل على ظهور اقل حدة لأعراض الانسحاب و للرغبة في العودة إلى التعاطي بالمقارنة بالطريقتين الأخرتين و كذلك معدل الإنتكاسة كان أقل بإستخدام الطريقة الاولى و على ذلك فإنه يمكن استنتاج أن استخدام عقار الفلومازينيل مع جرعات منخفضة من عقار الأوكسازيبام فى الثلاث ليالي الأولى من العلاج تبدو انها اكثر فاعلية فى التحكم فى أعراض الانسحاب و تقليص الرغبة فى العودة الى التعاطى و كذلك معدل الإنتكاسة بالمقارنة بتناول الأوكسازيبام أو التوقف المفاجىء للبنزوديازيبين مع العلاج العرضى.