

UDK 37

ISSN 2545 - 4439
ISSN 1857 - 923X

INTERNATIONAL JOURNAL

Institute of Knowledge Management

KNOWLEDGE



Scientific Papers

Vol. 31. 4.

MEDICAL SCIENCES AND HEALTH



KIJ

Vol. 31

No. 4

pp. 811 - 1198

Skopje 2019

Global Impact & Quality Factor 1.822 (2107) <http://globalimpactfactor.com/knowledge-international-journal/>

KNOWLEDGE – International Journal

Vol.31.4

June, 2019

KNOWLEDGE



INTERNATIONAL JOURNAL

**SCIENTIFIC PAPERS
VOL. 31.4**

*Promoted in Budva, Montenegro
June, 2019*



KNOWLEDGE

International Journal Scientific papers Vol. 31.4

ADVISORY BOARD

Vlado Kambovski PhD, Robert Dimitrovski PhD, Siniša Zarić PhD, Maria Kavdanska PhD, Venelin Terziev PhD, Mirjana Borota – Popovska PhD, Cezar Birzea PhD, Ljubomir Kekenovski PhD, Veselin Videv PhD, Ivo Zupanovic, PhD, Savo Ashtalkoski PhD, Zivota Radosavljević PhD, Laste Spasovski PhD, Mersad Mujevic PhD, Nonka Mateva PhD, Rositsa Chobanova PhD, Predrag Trajković PhD, Dzulijana Tomovska PhD, Nedžad Korajlić PhD, Nebojsa Pavlović PhD, Nikolina Ognenska PhD, Baki Koleci PhD, Lisen Bashkurti PhD, Trajce Dojcinovski PhD, Jana Merdzanova PhD, Zoran Srzentić PhD, Nikolai Sashkov Cankov PhD, Marija Kostic PhD

Print: GRAFOPROM – Bitola

Editor: IKM – Skopje

Editor in chief

Robert Dimitrovski, PhD

KNOWLEDGE - International Journal Scientific Papers Vol. 31.4

ISSN 1857-923X (for e-version)

ISSN 2545 – 4439 (for printed version)

INTERNATIONAL EDITORIAL BOARD

President: Academic, Prof. Vlado Kambovski PhD, Skopje (Macedonia)

Vice presidents:

Prof. Robert Dimitrovski PhD, Institute of Knowledge Management, Skopje (Macedonia)

Prof. Sinisa Zaric, PhD, Faculty of Economics, University of Belgrade, Belgrade (Serbia)

Prof. Venelin Terziev PhD, University of Rousse, Rousse (Bulgaria)

Prof. Mersad Mujevic PhD, Public Procurement Administration of Montenegro (Montenegro)

Prof. Tihomir Domazet PhD, President of the Croatian Institute for Finance and Accounting, Zagreb (Croatia)

Members:

- Prof. Aleksandar Korablev PhD, Dean, Faculty for economy and management, Saint Petersburg State Forest Technical University, Saint Petersburg (Russian Federation)
- Prof. Azra Adjajlic – Dedovic PhD, Faculty of criminology and security, Sarajevo (Bosnia & Herzegovina)
- Prof. Anita Trajkovska PhD, Rochester University (USA)
- Prof. Anka Trajkovska-Petkoska PhD, UKLO, Faculty of technology and technical sciences, Bitola (Macedonia)
- Prof. Alisabri Sabani PhD, Faculty of criminology and security, Sarajevo (Bosnia & Herzegovina)
- Prof. Ahmad Zakeri PhD, University of Wolverhampton, (United Kingdom)
- Prof. Ana Dzumalieva PhD, South-West University “Neofit Rilski”, Blagoevgrad (Bulgaria)
- Prof. Aziz Pollozhani PhD, Rector, University Mother Teresa, Skopje (Macedonia)
- Prof. Branko Sotirov PhD, University of Rousse, Rousse (Bulgaria)
- Prof. Branko Boshkovic, PhD, College of Sports and Health, Belgrade (Serbia)
- Prof. Branimir Kampl PhD, Institute SANO, Zagreb (Croatia)
- Prof. Baki Koleci PhD, University Hadzi Zeka, Peja (Kosovo)
- Prof. Branislav Simonovic PhD, Faculty of Law, Kragujevac (Serbia)
- Prof. Bistra Angelovska, Faculty of Medicine, University “Goce Delcev”, Shtip (Macedonia)
- Prof. Cezar Birzea, PhD, National School for Political and Administrative Studies, Bucharest (Romania)
- Prof. Cvetko Andreevski, Dean, Faculty of Tourism, UKLO, Bitola (Macedonia)
- Prof. Drago Cvijanovic, PhD, Faculty of Hotel Management and Tourism, University of Kragujevac, Vrnjacka Banja (Serbia)
- Prof. Dusan Ristic, PhD Emeritus, College of professional studies in Management and Business Communication, Novi Sad (Serbia)
- Prof. Dimitar Radev, PhD, Rector, University of Telecommunications and Post, Sofia (Bulgaria)
- Prof. Daniela Todorova PhD, Rector of “Todor Kableshev” University of Transport, Sofia (Bulgaria)
- Prof. Dragan Kokovic PhD, University of Novi Sad, Novi Sad (Serbia)
- Prof. Dragan Marinkovic PhD, High health – sanitary school for professional studies, Belgrade (Serbia)
- Prof. Daniela Ivanova Popova PhD, Faculty of Public Health and Sport, SWU Neofit Rilski, Blagoevgrad (Bulgaria)
- Prof. Dzulijana Tomovska, PhD, Dean, Faculty of Biotechnical sciences, Bitola (Macedonia)
- Prof. Evgenia Penkova-Pantaleeva PhD, UNWE -Sofia (Bulgaria)

-
- Prof. Fadil Millaku, PhD, Rector, University “Hadzi Zeka”, Peja (Kosovo)
 - Prof. Fatos Ukaj, University “Hasan Prishtina”, Prishtina (Kosovo)
 - Prof. Georgi Georgiev PhD, National Military University “Vasil Levski”, Veliko Trnovo (Bulgaria)
 - Prof. Halit Shabani, PhD, University “Hadzi Zeka”, Peja (Kosovo)
 - Prof. Halima Sofradzija, PhD, University of Sarajevo, Sarajevo (Bosnia and Herzegovina)
 - Prof. Haris Halilovic, Faculty of criminology and security, University of Sarajevo, Sarajevo (Bosnia and Herzegovina)
 - Prof. Helmut Shramke PhD, former Head of the University of Vienna Reform Group (Austria)
 - Prof. Hristina Georgieva Yancheva, PhD, Rector, Agricultural University, Plovdiv (Bulgaria)
 - Prof. Hristo Beloev PhD, Bulgarian Academy of Science, Rector of the University of Rousse (Bulgaria)
 - Prof. Hristina Milcheva, Medical college, Trakia University, Stara Zagora (Bulgaria)
 - Prof. Izet Zeqiri, PhD, Academic, SEEU, Tetovo (Macedonia)
 - Prof. Ivan Marchevski, PhD, Rector, D.A. Tsenov Academy of Economics, Svishtov (Bulgaria)
 - Doc. Igor Stubelj, PhD, PhD, Faculty of Management, Primorska University, Koper (Slovenia)
 - Prof. Ivo Zupanovic, PhD, Faculty of Business and Tourism, Budva (Montenegro)
 - Prof. Ivan Petkov PhD, Rector, European Polytechnic University, Pernik (Bulgaria)
 - Prof. Isa Spahiu PhD, AAB University, Prishtina (Kosovo)
 - Prof. Ivana Jelik PhD, University of Podgorica, Faculty of Law, Podgorica (Montenegro)
 - Prof. Islam Hasani PhD, Kingston University (Bahrein)
 - Prof. Jova Ateljevic PhD, Faculty of Economy, University of Banja Luka, (Bosnia & Herzegovina)
 - Prof. Jove Kekenovski PhD, Faculty of Tourism, UKLO , Bitola (Macedonia)
 - Prof. Jonko Kunchev PhD, University „Cernorizec Hrabar“ - Varna (Bulgaria)
 - Prof. Jelena Stojanovic PhD, High medicine school for professional studies “Hipokrat”, Bujanovac (Serbia)
 - Prof Karl Schopf, PhD, Akademie fur wissenschaftliche forchung und studium, Wien (Austria)
 - Prof. Katerina Belichovska, PhD, Faculty of Agricultural Sciences, UKIM, Skopje (Macedonia)
 - Prof. Krasimir Petkov, PhD, National Sports Academy “Vassil Levski”, Sofia (Bulgaria)
 - Prof. Kamal Al-Nakib PhD, College of Business Administration Department, Kingdom University (Bahrain)
 - Prof. Kiril Lisichkov, Faculty of Technology and Metallurgy, UKIM, Skopje (Macedonia)
 - Prof. Lidija Tozi PhD, Faculty of Pharmacy, Ss. Cyril and Methodius University, Skopje (Macedonia)
 - Prof. Laste Spasovski PhD, Vocational and educational centre, Skopje (Macedonia)
 - Prof. Larisa Velic, PhD, Faculty of Law, University of Zenica, Zenica (Bosnia and Herzegovina)
 - Prof. Lujza Grueva, PhD, Faculty of Medical Sciences, UKIM, Skopje (Macedonia)
 - Prof. Lazar Stosic, PhD, Association for development of science, engineering and education, Vranje (Serbia)
 - Prof. Lisen Bashkurti PhD, Global Vice President of Sun Moon University (Albania)
 - Prof. Lence Mircevska PhD, High Medicine School, Bitola, (Macedonia)
 - Prof. Ljubomir Kekenovski PhD, Faculty of Economics, UKIM, Skopje (Macedonia)
 - Prof. Ljupce Kocovski PhD, Faculty of Biotechnical sciences, Bitola (Macedonia)

-
- Prof. Marusya Lyubcheva PhD, University “Prof. Asen Zlatarov”, Member of the European Parliament, Burgas (Bulgaria)
 - Prof. Maria Kavdanska PhD, Faculty of Pedagogy, South-West University Neofit Rilski, Blagoevgrad (Bulgaria)
 - Prof. Maja Lubenova Cholakova PhD, Faculty of Public Health and Sport, SWU Neofit Rilski, Blagoevgrad (Bulgaria)
 - Prof. Mirjana Borota-Popovska, PhD, Centre for Management and Human Resource Development, Institute for Sociological, Political and Juridical Research, Skopje (Macedonia)
 - Prof. Mihail Garevski, PhD, Institute of Earthquake Engineering and Engineering Seismology, Skopje (Macedonia)
 - Prof. Misho Hristovski PhD, Faculty of Veterinary Medicine, Ss. Cyril and Methodius University, Skopje (Macedonia)
 - Prof. Mitko Kotovchevski, PhD, Faculty of Philosophy, UKIM, Skopje (Macedonia)
 - Prof. Milan Radosavljevic PhD, Dean, Faculty of strategic and operational management, Union University, Belgrade (Serbia)
 - Prof. Marija Topuzovska-Latkovikj, PhD, Centre for Management and Human Resource Development, Institute for Sociological, Political and Juridical Research, Skopje (Macedonia)
 - Prof. Marija Knezevic PhD, Academic, Banja Luka, (Bosnia and Herzegovina)
 - Prof. Margarita Bogdanova PhD, D.A.Tsenov Academy of Economics, Svishtov (Bulgaria)
 - Prof. Mahmut Chelik PhD, Faculty of Philology, University “Goce Delchev”, Shtip (Macedonia)
 - Prof. Marija Mandaric PhD, Faculty of Hotel Management and Tourism, University of Kragujevac, Vrnjacka Banja (Serbia)
 - Prof. Marina Simin PhD, College of professional studies in Management and Business Communication, Sremski Karlovci (Serbia)
 - Prof. Miladin Kalinic, College of professional studies in Management and Business Communication, Sremski Karlovci (Serbia)
 - Prof. Mitre Stojanovski PhD, Faculty of Biotechnical sciences, Bitola (Macedonia)
 - Prof. Miodrag Smelcerovic PhD, High Technological and Artistic Vocational School, Leskovac (Serbia)
 - Prof. Nadka Kostadinova, Faculty of Economics, Trakia University, Stara Zagora (Bulgaria)
 - Prof. Natalija Kirejenko PhD, Faculty For economic and Business, Institute of Entrepreneurial Activity, Minsk (Belarus)
 - Prof. Nenad Taneski PhD, Military Academy “Mihailo Apostolski”, Skopje (Macedonia)
 - Prof. Nevenka Tatkovic PhD, Juraj Dobrila University of Pula, Pula (Croatia)
 - Prof. Nedžad Korajlic PhD, Dean, Faculty of criminal justice and security, University of Sarajevo (Bosnia and Herzegovina)
 - Prof. Nikolay Georgiev PhD, “Todor Kableshkov” University of Transport, Sofia (Bulgaria)
 - Prof. Nikolina Ognenska PhD, Faculty of Music, SEU - Blagoevgrad (Bulgaria)
 - Prof. Nishad M. Navaz PhD, Kingdom University (India)
 - Prof. Oliver Iliev PhD, Faculty of Communication and IT, FON University, Skopje (Macedonia)
 - Prof. Oliver Dimitrijevic PhD, High medicine school for professional studies “Hipokrat”, Bujanovac (Serbia)
 - Prof. Paul Sergius Koku, PhD, Florida State University, Florida (USA)
 - Prof. Primoz Dolenc, PhD, Faculty of Management, Primorska University, Koper (Slovenia)
 - Prof. Predrag Trajkovic PhD, JMPNT, Vranje (Serbia)
 - Prof. Petar Kolev PhD, “Todor Kableshkov” University of Transport, Sofia (Bulgaria)
 - Prof. Pere Tumbas PhD, Faculty of Economics, University of Novi Sad, Subotica (Serbia)

- Prof. Rade Ratkovic PhD, Faculty of Business and Tourism, Budva (Montenegro)
- Prof. Rositsa Chobanova PhD, University of Telecommunications and Posts, Sofia (Bulgaria)
- Prof. Rumen Valcovski PhD, Imunolab Sofia (Bulgaria)
- Prof. Rumen Stefanov PhD, Dean, Faculty of public health, Medical University of Plovdiv (Bulgaria)
- Prof. Sasho Korunoski, Rector, UKLO, Bitola (Macedonia)
- Prof. Sashko Plachkov PhD, Faculty of Pedagogy, University Neofit Rilski, Blagoevgrad (Bulgaria)
- Prof. Snezhana Lazarevic, PhD, College of Sports and Health, Belgrade (Serbia)
- Prof. Stojan Ivanov Ivanov PhD, Faculty of Public Health and Sport, SWU Neofit Rilski, Blagoevgrad (Bulgaria)
- Prof. Snezana Stoilova, PhD, High Medicine School, Bitola, (Macedonia)
- Prof. Stojna Ristevska PhD, High Medicine School, Bitola, (Macedonia)
- Prof. Suzana Pavlovic PhD, High health – sanitary school for professional studies, Belgrade (Serbia)
- Prof. Sandra Zivanovic, PhD, Faculty of Hotel Management and Tourism, University of Kragujevac, Vrnjacka Banja (Serbia)
- Prof. Shyqeri Kabashi, College “Biznesi”, Prishtina (Kosovo)
- Prof. Trayan Popkochev PhD, Faculty of Pedagogy, South-West University Neofit Rilski, Blagoevgrad (Bulgaria)
- Prof. Todor Krystevich, Vice Rector, D.A. Tsenov Academy of Economics, Svishtov (Bulgaria)
- Prof. Todorcka Atanasova, Faculty of Economics, Trakia University, Stara Zagora (Bulgaria)
- Doc. Tatyana Sobolieva PhD, State Higher Education Establishment Vadiym Getman Kiyev National Economic University, Kiyev (Ukraine)
- Prof. Tzako Pantaleev PhD, NBUniversity , Sofia (Bulgaria)
- Prof. Violeta Dimova PhD, Faculty of Philology, University “Goce Delchev”, Shtip (Macedonia)
- Prof. Volodymyr Denysyuk, PhD, Dobrov Center for Scientific and Technological Potential and History studies at the National Academy of Sciences of Ukraine (Ukraine)
- Prof. Valentina Staneva PhD, “Todor Kableshkov” University of Transport, Sofia (Bulgaria)
- Prof. Vasil Zecev PhD, College of tourism, Blagoevgrad (Bulgaria)
- Prof. Venus Del Rosario PhD, Arab Open University (Philippines)
- Prof. Yuri Doroshenko PhD, Dean, Faculty of Economics and Management, Belgorod (Russian Federation)
- Prof. Zlatko Pejkovski, PhD, Faculty of Agricultural Sciences, UKIM, Skopje (Macedonia)
- Prof. Zivota Radosavljevik PhD, Dean, Faculty FORCUP, Union University, Belgrade (Serbia)
- Prof. Zorka Jugovic PhD, High health – sanitary school for professional studies, Belgrade (Serbia)

REVIEW PROCEDURE AND REVIEW BOARD

Each paper is reviewed by the editor and, if it is judged suitable for this publication, it is then sent to two referees for double blind peer review.

The editorial review board is consisted of 45 members, full professors in the fields 1) Natural and mathematical sciences, 2) Technical and technological sciences, 3) Medical sciences and Health, 4) Biotechnical sciences, 5) Social sciences, and 6) Humanities from all the Balkan countries and the region.

CONTENTS

ETYMOLOGY OF CIRCULAR CARIES	829
Olga Kokoceva-Ivanovska	829
Efka Zabokova-Bilbilovska	829
Mijoska Aneta.....	829
BIOCOMPATIBILITY AND REACTION OF DENTAL POLYMERS IN ORAL ENVIRONMENT .	835
Natasha Stavreva	835
Biljana Kapusevska	835
STUDY OF THE SIZE OF THE ANGLE OF THE MANDIBLE.....	841
Svetlana Jovevska.....	841
Mihajlo Petrovski	841
DENTAL SCANNERS IN PROSTHODONTICS	845
Blagoja Dashtevski	845
Aneta Mijoska.....	845
Marjan Petkov.....	845
Vanco Spirov	845
Oliver Dimitrovski.....	845
TEETH EXTRACTION WITH ROOT DELACERATION ON THE ORTHODONTIC INDICATIONS	
.....	853
Pavel Stanimirov.....	853
Greta Yordanova.....	853
DIFFERENCE IN CRANIOFACIAL CHARACTERISTICS IN ATTRACTIVE MALE AND FEMALE	
FACES	859
Sofija Carceva Shalja.....	859
Sandra Atanasova	859
Mihajlo Petrovski	859
ORAL TISSUE CONDITION IN PROSTHODONTIC GERIATRIC PATIENTS	865
Aneta Mijoska.....	865
Gordana Kovacevska	865
Georgi Tomov.....	865
INTRODUCTION TO ORTHODONTIC EDUCATION IN BULGARIA OF DIGITAL	
TECHNOLOGIES AND 3D ARCHIVING	869
Greta Yordanova.....	869
Martin Mladenov	869
INDICATIONS FOR MOLAR EXTRACTION DURING ORTHODONTIC TREATMENT.....	873
Sandra Atanasova	873
Sofija Carceva Salja.....	873
Ljubica Prosheva	873
COMPOSITE RESTORATIONS IN DENTISTRY.....	879
Aleksandar Andreevski.....	879
INFLUENCE OF GROWTH IN TREATED CLASS III GROWING PATIENTS WITH FACE MASK	
THERAPY AND UNTREATED PATIENTS.....	883
Sofija Carceva Shalja.....	883
Sandra Atanasova	883
POSITION OF THE MENTAL FORAMEN IN CORELATION WITH THE LOWER PREMOLARS: A	
PANORAMIC RADIOGRAPHIC STUDY	889
Mihajlo Petrovski	889
Svetlana Jovevska.....	889
Olivera Terzieva-Petrovska	889

PREVALENCE OF DENTAL CARIES IN CORRELATION WITH ORAL HYGIENE	895
Ivona Kovacevska.....	895
Natasha Longurova.....	895
Katerina Zlatanovska.....	895
THE SIGNIFICANCE OF TRAINING AND EDUCATION IN ACCURATE EVALUATION OF NATURAL TOOTH COLOR	901
Juliya Zarkova	901
Ivan Nacevski	901
Vesna Korunovska Stefkovska	901
FUNCTIONAL RECOVERY OF VOICE FUNCTION IN PATIENTS WITH LARYNGEAL DYSFUNCTION: OBSERVATIONAL STUDY	905
Galina Mratskova	905
Damyam Petrov	905
THE INFLUENCE OF HYPERPROLACTINEMIA ON THE LEVEL OF FSH AND LH IN WOMEN	911
Mire Spasov.....	911
Verica Spasova	911
ACREDITED MOLECULAR METHODS FOR DETECTION OF INFECTIONS CAUSED BY HIV, HEPATITIS B VIRUS AND HEPATITIS C VIRUS	917
Belinda Gelmanovska.....	917
Vaso Taleski	917
FLUORESCENT IN SITU HYBRIDIZATION AND IMMUNOHISTOCHEMISTRY FOR SUBTYPING “NON-CLASSIFIABLE” RENAL CELL CARCINOMAS	921
Atanas Ivanov	921
Vili Stoyanova	921
JEJUNAL ADENOCARCINOMA: A CASE REPORT	925
Gordana Bozhinovska Beaka.....	925
Biljana Prgova Veljanovska	925
Milka Zdravkovska.....	925
Irena Eftimovska Rogac	925
Nadica Bozhinovska	925
THE ROLE OF TUMOR MARKERS CA 125, CA 72-4 AND CA 19-9 IN DETECTION AND MONITORING OF THE COURSE OF DISEASE OF OVARIAN CARCINOMA AND CARCINOMA OF THE UTERINE BODY	931
Kristina Petkova	931
Venci Chalkov	931
SPLenic ABSCESS IN PATIENT WITH CHRONIC PANCREATITIS: A CASE REPORT	937
Gordana Bozhinovska Beaka.....	937
Biljana Noveska-Petrovska.....	937
Biljana Prgova Veljanovska	937
Nadica Bozhinovska	937
ROLE OF GOUT IN ATRIAL FIBRILLATION.....	943
Antoniya Kisheva	943
DEVELOPMENT ROLE AND IMPORTANCE OF FETAL AUTOPSY SCIENTIFIC PURPOSES - REVIEW OF THE LITERATURE.....	947
Tanya Kitova	947
BARRIERS TO THE EFFECTIVENESS OF DISEASE MANAGEMENT IN PEOPLE WITH DIABETES MELLITUS	953
Boryana Levterova	953

DYABETTE CONTROL PROGRAM AND PREVENTION OF THEIR CONDITIONS - PROPOSALS AND GUIDELINES	959
Varvara Pancheva.....	959
Valentin Vassilev.....	959
ALGORITHM OF COMPLEX PROGRAM FOR TREATMENT AND REHABILITATION IN DEGENERATIVE DISEASES OF THE VERTEBRAL COLUMN IN THE CERVICAL AREA. PREVENTION OF CERVICAL ARTHROPATHY	963
Petya Kasnakova.....	963
THE DIAGNOSIS OF DAUCUS CAROTA AS ALERGOGEN ON THE IMMUNE SYSTEM IN WHITE LABORATORY RAT	969
Mire Spasov.....	969
Icko Gjorgoski	969
THE DIAGNOSIS OF PHLEUM PRATENSE AS ALERGOGEN ON THE IMMUNE SYSTEM IN WHITE LABORATORY RAT	975
Hristijan Spasov.....	975
Mire Spasov.....	975
Icko Gjorgoski	975
Majlinda Ademi.....	975
INCREASED MEASLES MORBIDITY AND PUBLIC AWARENESS OF THE RISKS OF REFUSING IMMUNIZATION FOR THIS DISEASE	981
Ivelina Dobрева	981
Pavlina Teneva	981
Tsvetana Bojkova	981
PERSPECTIVES IN HEALTH CARE FOR CHILDREN WITH SPECIAL NEEDS IN CHILDREN'S AND SCHOOL HEALTH.....	985
Monika Obreykova.....	985
Galina Terzieva.....	985
MYOPIA IN PRE-SCHOOL CHILDREN AND MOBILE PHONES	991
Aleksandar Dodevski.....	991
Strahil Gazepov	991
Biljana Dodevska.....	991
Alen Georgijev	991
VISUAL SCREENING OF SCHOOL CHILDREN IN THE MUNICIPALITY OF SAPAREVA BANYA IN SOUTHWESTERN BULGARIA.....	995
Slavena Stoykova	995
Ekaterina Petrova.....	995
WETTABILITY – ANOTHER PARAMETER FOR GOOD FITTING OF A SILICONE-HYDROGEL DAILY DISPOSABLE CONTACT LENS	1001
Nikola Peev	1001
SUCCESSFUL COGNITIVE AGING - COGNITIVE RESERVE AND NEUROPLASTICITY	1005
Antonia Yaneva	1005
Kristina Kilova	1005
Teodora Dimcheva	1005
THE ROLE OF ACUPUNCTURE IN THE REHABILITATION OF PARALYSIS OF N.FACIALIS	1009
Lence Nikolovska	1009
Stefanija Gjorgieva.....	1009
Mire Spasov.....	1009

NEED FOR TRAINING OF HEALTHCARE PROFESSIONALS FROM OUTPATIENT CARE FOR BURNS INJURIES	1013
Anushka Dimitrova.....	1013
CARE AND TREATMENT IN PATIENTS WITH HEPATITIS B IN THE MUNICIPALITY OF PRILEP	1019
Panova Gordana.....	1019
Boshevska Viktorija	1019
Liljana Simonovska	1019
Iva Paneva	1019
Lenche Nikolovska	1019
Mire Spasov	1019
Gjorgji Shumanov.....	1019
ACUTE VENLAFAXINE OVERDOSE WITH POSITIVE URINE IMMUNOASSAY FOR TRAMADOL – CLINICAL AND DIAGNOSTIC OVERLAP - CASE REPORT AND LITERATURE OVERVIEW	1027
Pereska Zanina.....	1027
Janicevic-Ivanovska Danijela	1027
Bekjarovski Niko.....	1027
Simonovska Natasha.....	1027
Babulovska Aleksandra	1027
DRUG-INDUCED NEUTRALIZING ANTIBODIES TO TNF- α BLOCKES IN PATIENTS WITH INFLAMMATORY JOINT DISEASES FOLLOWED BY 24-MONTHS.....	1033
Krassimir Kraev.....	1033
Mariela Geneva-Popova	1033
Velichka Popova.....	1033
Stanislava Popova.....	1033
INFORMATION AND KNOWLEDGE OF THE ANTIBIOTICS AND THE ANTIBIOTIC RESIDENCE OF THE POPULATION FROM THE SOUTHEAST REGION OF REPUBLIC OF NORTH MACEDONIA	1039
Milka Zdravkovska.....	1039
Marija Darkovska-Serafimovska	1039
Gordana Bozinovska-Beaka	1039
Svetlana Zivkova	1039
SIMPLE LIQUID CHROMATOGRAPHY METHOD WITH UV DETECTION FOR DETERMINATION OF BROMAZEPAM IN SOLID PHARMACEUTICAL DOSAGE FORMS	1045
Irena Brcina	1045
Marija Darkovska Serafimovska	1045
Tijana Serafimovska	1045
Trajan Balkanov	1045
Biljana Gjorgjeska.....	1045
CONSUMPTION ANALYSIS OF MOST PRESCRIBED ANTIBIOTICS FINANCED BY THE HEALTH INSURANCE FUND IN REPUBLIC OF NORTH MACEDONIA	1051
Elena Drakalska.....	1051
Bistra Angelovska.....	1051
Veneta Zdravkova.....	1051
MICROBIOLOGICAL DIAGNOSIS AND IMPORTANCE OF INFECTIONS CAUSED BY INFLENZAE – A VIRUS	1057
Zivadinka Cvetanovska	1057
Vaso Taleski	1057

POISONOUS SNAKES OF BULGARIA: CLINICAL AND EPIDEMIOLOGICAL ANALYSIS	1063
Olimpiada Atmazhova	1063
Evgenia Barzashka	1063
Iskra Petkova	1063
BODY FAT DISTRIBUTION AND LIPID PROFILE CHANGES AFTER WEIGHT LOSS – A CASE REPORT	1071
Slavica Shubeska Stratrova	1071
Danijela Janicevic Ivanovska	1071
FACTORS FOR OBESITY IN STUDENTS FROM THE SCHOOLS	1077
Antoaneta Grozeva	1077
INFLUENCE OF SUNSHINE ON THE SERUM LEVELS OF VITAMIN D	1081
Ivelina Dobрева	1081
Pavlina Teneva	1081
Valya Trencheva.....	1081
GEOMEDICAL TOURISM – OUTDOOR HEALTH CARE FACILITIES ANTI-GEOPATHIC STRESS TREATMENT	1087
Krasimira Staneva.....	1087
APPLICATION OF BLASTWARE SOFTWARE FOR MEASURING MICROCOLIMIC CONDITIONS	1093
Naim Baftiu	1093
Raif Bytyqi	1093
Overall, the number of measurements	1096
Percentage	1096
APPLICATION OF BIOPRINTING IN CONTEMPORARY MEDICINE (REVIEW).....	1099
Desislava Bakova	1099
Kristina Kilova	1099
Maria Semerdjieva.....	1099
CBRN EVENT - DO WE NEED MEDICAL INTELLIGENCE.....	1103
Elena Valkanova.....	1103
Rostislav Kostadinov.....	1103
ACUTE PANCREATITIS	1107
Redzep Emurlai	1107
PALLIATIVE CARE AND EUTHANASIA – CONVERGENCE POINTS AND PUBLIC ATTITUDES	1113
Nikola Sabev.....	1113
SOCIOECONOMIC CHARACTERISTICS OF PATIENTS WITH TENSION HEADACHE IN MUNICIPALITY OF VELES	1119
Elena Manchevska.....	1119
Toshe Krstev.....	1119
Gordana Panova.....	1119
SEASONALITY IN THE APPEARANCE OF INTRA HOSPITAL INFECTIONS	1127
Emilija Chapevska.....	1127
PEDAGOGICAL COMPETENCE OF MENTORS DURING THE PRE-GRADUATION TRAINEESHIP OF FUTURE NURSES	1131
Snezhana Dragusheva.....	1131
Penka Petleshkova.....	1131
Tanya Paskaleva	1131

ACUTE VENLAFAXINE OVERDOSE WITH POSITIVE URINE IMMUNOASSAY FOR TRAMADOL – CLINICAL AND DIAGNOSTIC OVERLAP - CASE REPORT AND LITERATURE OVERVIEW

Pereska Zanina

University Clinic of Toxicology, Medical Faculty-Skopje, SS Cyril and Methodius University, R. North Macedonia perevska@yahoo.com

Janicevic-Ivanovska Danijela

University Clinic of Biochemistry, Clinical Campus Mother Theresa, University Goce Delchev Shtip, R. North Macedonia, djanicevic@yahoo.com

Bekjarovski Niko

University Clinic of Toxicology, Medical Faculty-Skopje SS Cyril and Methodius University, R. North Macedonia nikobekarovski@gmail.com

Simonovska Natasha

University Clinic of Toxicology, Medical Faculty-Skopje SS Cyril and Methodius University, Skopje, R. North Macedonia n.simonovska@yahoo.com

Babulovska Aleksandra

University Clinic of Toxicology, Medical Faculty, SS Cyril and Methodius University, 1000 Skopje, R. North Macedonia ababulovska@yahoo.com

Abstract: Objective. The overlapping of pharmacokinetics and/or the pharmacodynamics of medicines causes the occurrence of overlapping clinical syndromes and diagnostic issues, potentiated in overdoses. We report a case of severe venlafaxine poisoning where the clinical presentation and the results of rapid immunoassay test overlapped with tramadol intoxication.

Case presentation. An unconscious women with recurrent seizers, hypertension and supposed acute medication poisoning in suicidal attempt was transported to our clinic. Previously, she had been lavaged, rehydrated and treated with 20 mg diazepam iv, 40 mg furosemide at the local general hospital. Her regular tablet therapy consisted of losartan, levothyroxine, venlafaxine, occasionally tramadol.

At admission she was comatose, with isochoric normal pupils, BP 130/80 mm Hg, SaO₂ 86%, and recurrent episodes of seizures treated with 10mg diazepam iv, ocular clonus, hypertonus, temperature 38.9C, diaphoresis, facial hyperaemia, dark coloured urine, hyponatremia and rhabdomyolysis. The lateral flow immunoassay (AbuGnostR) was positive for tramadol, but the homogeneous enzyme immunoassay did not confirm it. After 36 hours of intensive treatment she became somnolent and reported ingestion of 2250 mg tbl Venlafaxine. The AbuGnost R test detects tramadol at cut off urine values 200ng/ml, but present cross reactivity with O-desmethyl-venlafaxine at cut off values up to 25000ng/ml. The following days she complained of muscular weakness, headaches and cognitive impairment, which lasted for more then one month after release from hospital.

Conclusion. High concentrations of venlafaxine metabolites induce false positive tramadol immunoassay (AbuGnostR) test. Overlapping clinical presentations and metabolic pathways of venlafaxine and tramadol should alert physicians when interpret rapid immunoassay test. The mandatory principle when making medical decisions should cover synthesis of critically interpreted toxicology analysis, interview data and clinical features of the poisoning, which may help to avoid misleading conclusions and improve the diagnostic and therapy decisions.

Keywords: venlafaxine, tramadol, poisoning, lateral flow immunoassay,

1.INTRODUCTION

Venlafaxine is an antidepressant acting as a serotonin and norepinephrine reuptake inhibitor and weak inhibitor of dopamine reuptake. The reported poisonings with venlafaxine showed lower toxicity compared to TCA, but higher than SSRIs. The complexity of treatment decisions-making for these poisonings is associated not only with the disproportionate poisoning severity to the ingestion dose (Fischer, Unterecker, & Pfuhlmann, 2012) and overlapping clinical syndromes with other serotonin and/or norepinephrine reuptake inhibitors, but also with the necessity for rapid diagnosis in clinical practice and a high likelihood of false positives of rapid immunoassay tests (Saitman, Park, & Fitzgerald, 2014).

We report a case of severe venlafaxine poisoning which clinical presentation and rapid immunoassay test (LFIA-lateral flow immunoassay) overlapped with tramadol intoxication.

2. CASE REPORT

A middle aged women was admitted at the clinic after two prolonged episodes of seizures and supposed acute poisoning with medicines in suicidal attempt. She had a history of hypothyreosis, regularly treated with tablet (tbl) euthyrox (75 mg/day), hypertension treated with tbl losartan (50mg/day), depression treated with tbl. venlafaxine 75 mg/day and traumatic injury of the right ankle and foot treated with capsule tramadol a 50 mg occasionally. After her family found her unconscious, she was taken to the local general hospital where gastric lavage was performed and crystalloids were administered. After half an hour she had seizures lasting a couple of minutes. The second episode of seizures was associated with dramatic increase of blood pressure so 10 mg diazepam intravenously (iv) with 40 mg furosemide intramuscularly (im) were administered and she was transferred to our Clinic. During the transportation she received additional 10 mg diazepam im. because of new episode of seizures.

At admission she was comatose, with isochoric pupils, BP 130/80 mm Hg, SaO₂ 86% with clear lungs, soft abdomen and electrocardiogram (ECG) with sinus rhythm HR 95/min, QRS 105msec, QTc 437msec, non ischemic (ascendant) ST elevation.

Soon, she had another episode of seizures associated with more severe hypoxemia (75%) treated with diazepam 10 mg iv and gradually she developed ocular clonus, with hypertonus, increased temperature 38.9C and diaphoresis with facial hyperaemia. Urinary catheter insertion revealed dark urine.

Laboratory findings showed increased white blood counts, creatine kinase (CK), myoglobin and severe hyponatremia 111mmol/l (137-145 mmol/l referent values). Serum analysis: BUN, creatinine, glycemia, bilirubinemia, alkaline phosphatase, gamma-glutamyltransferase, calcium were in referent range during the whole hospital stay of the patient (Table 1).

Table 1. Laboratory findings during hospital stay

Parameter	Day 1	Day2	Day3	Day4	Day6	Day 8	Referent
Le x10 ⁹ /l	23.6	17,3	10,6	10,4	6,3	7,1	4-11
AST (U/l)	31	32	38		67	29	10-34
ALT (U/l)	20	19	22		67	46	10-45
LDH (U/l)	392	276	254		223	209	<248
Na (mmol/l)	109	120	135		137	136	137-145
K (mmol/l)	3,6	3,6	3,4		3,4	3,9	3,8-5,5
CRP (mg/l)	0,6	29,9	68,1		7,1	1,9	<6
CK (U/l)	452	525		4234	1409		24-173
CK-MB (U/l)	33			40			<25
Myoglobin (ng/ml)	351	/	277	601	227	57	10-46
Troponin (ng/l)	1,3	/	7,3	6,1	/	/	<15,6

AST-Aspartate aminotransferase, ALT- Alanine aminotransferase, LDH-Lactate dehydrogenas, CRP-C-reactive protein, CK-Creatine kinase, CK-MB- Cretaine kinase-MB

The urine screening test (LFIA-AbuGnostR-BioGnost) for tramadol was positive on initial presentation. The patient was treated with crystalloids (0,9% NaCl) with dose regime 2.5 mL/kg/h IV infusion, hypertonic sodium (according Joint European Guidelines), sodium hydrogen bicarbonate (1mmol/kg i.v), diazepam 0.20mg/kg iv, ceftriaxone 2gr/day.

After 36 hours of intensive therapy and after serum concentrations of sodium were normalised, the seizures ceased. The patient was somnolent, complained of muscular weakness, difficulties in self-standing from bed and upright standing, spasm of jaw muscles, headaches, with cognitive difficulties and disorientation. She self- reported ingestion of 30 tbl venlafaxine 75mg. The re-analysis of the firstly collected urinary sample using homogenous enzyme immunoassay HEIA (Beckman coulter AU 480) excluded the presence of tramadol and its metabolites in the patient's urine. The following days gradual normalization of consciousness occurred but the headaches and cognitive deterioration persisted. Plasma levels of myoglobin reached their maximum on the fourth day of hospitalization with parallel existence of expressed muscle weakness in the same period. Treatment with intensive hydration, bicarbonates and diuretics enabled the preservation of renal function.

Consultative examination by the neurologist on the 4th day confirmed that there were no neither focal neurologic deficit nor meningeal irritation, but also noted that the patient was confused, disoriented with difficulties in maintaining contact. During the hospital stay she presented slow regression of the parameters of rhabdomyolysis with preserved renal function, and persistent cognitive impairment.

ECG at discharge presented sinus rhythm, HR 95/min, normal P wave, QRS 85msec, QTc 407msec, isoelectric ST segment.

A month after release from hospital, due to persistent headaches, selective amnesia, confusion, anxiety and insomnia, the patient was re-examined by a neurologist who excluded organic neurological suffering and deficit. She continued the treatment at the psychiatric unit.

3. DISCUSSION

There were several reports of cross-reactivity of venlafaxine with phencyclidine using rapid immunoassays (Bond, Steele, & Uges, 2003) but our presentation was first reporting of venlafaxine with tramadol cross reactivity using rapid LFIA test in acute venlafaxine overdose (VO). The goal of presenting this case is to provide a wider clinical context when interprets urine drug test results considering overlapping clinical presentation of venlafaxine poisoning with tramadol and reassessment of the inefficacy if antidote treatment (naloxone) was used in such poisonings.

Venlafaxine (antidepressant) and tramadol (analgesic) are prescribed for different medical indication but share many similarities in chemical structure, inhibition of serotonin and nor-adrenalin reuptake and metabolic pathway (Reeves & Cox, 2008). Even more, it was found that venlafaxine present analgesic effects (Jha, Mazumdar, & Bhatt, 2006) as well as tramadol have antidepressant activity (Kalra, Tayal, & Chawla, 2008). In our case, the patient was receiving concomitant treatment with tbl venlafaxine and occasionally cap. tramadol, according medical recommendation. Poisonings with venlafaxine as well as with tramadol induce overlapping clinical features, associated with their pharmacokinetic profile.

Rhabdomyolysis is a significant clinical feature of acute poisoning with antidepressants, especially with venlafaxine (Wilson, Howell, & Waring, 2007), but it is associated with acute tramadol poisoning too (Khan, Yousef, & Errayes, 2010). The laboratory findings confirmed the development of rhabdomyolysis with more than five time increase of CK (creatin phosphokinase) at the 4th day of hospitalisation and serum myoglobin as an early marker of myotoxicity (Melli, Chaudhry, & Cornblath, 2005). Myoglobinuria was not investigated in our patient due to the unavailable diagnostic tests, although some studies have found that the absence of urine myoglobin does not exclude rhabdomyolysis. Although, seizures are confounding factor for developing of rhabdomyolysis, the proposed underlying mechanism is direct myotoxic effects of venlafaxine, and also of tramadol poisoning (Rahimi, Soltaninejad, & Shadnia, 2014); the cardiac source of increased CK and myoglobin was excluded with ECG and normal troponin serum concentrations in our patient.

Hyponatremia (serum Na <135 mmol/l) is a serious electrolyte disturbance associated with poisoning with new generation of antidepressants including venlafaxine and tramadol poisoning (De Picker, Van Den Eede, Dumont, Moorkens, & Sabbe, 2014) too. Patients under diuretic therapy and elderly ones are at higher risk for hyponatremia, even in regular pharmacology doses (De Picker et al., 2014). The proposed mechanism is associated with serotonin reuptake inhibition, inducing either increased release of antidiuretic hormone (ADH) or increased sensitivity to ADH implying on syndrome of inappropriate secretion of ADH (De Picker et al., 2014). VO is associated with prominent hyponatremia (De Picker et al., 2014), even more pronounced than the poisonings with other types of SSRI. Our patient presented severe hyponatremia (<115 mmol/l) according Joint European Guidelines with life-threatening neurologic features (seizures, coma). Seizures cessation after correction of hyponatremia in our case was a clinical confirmation of the electrolyte imbalance as an underlying mechanism.

Serotonin syndrome (SS) in venlafaxine overdose is well documented in literature (Abadie et al., 2015). Although there was a suspicion that a tramadol poisonings causes SS (Ryan & Isbister, 2015), more studies have shown that tramadol overdose also induces the onset of SS (Tashakori & Afshari, 2010). SS is potentially life-threatening condition, confirmed in our patient according Hunter diagnostic criteria (Dunkley, Isbister, Sibbritt, Dawson, & Whyte, 2003). After complete clinical and laboratory restitution, the patient suffered from prolonged neurologic impairment, already reported in the literature considering VO.

The overlapping pharmacokinetic profile of venlafaxine and tramadol generates false positive results in diagnostic toxicological tests, too. The false positive result for tramadol LFIA in our patient resulted from the venlafaxine metabolite, O-desmethyl-venlafaxine which has similar transition to tramadol (O-desmethyl-tramadol) inducing cross-reactivity (Allen, 2006). The HEIA test from the same urine sample was negative for tramadol because has no cross-reactivity with venlafaxine and its metabolite O-desmethyl-venlafaxine; together with self-reported venlafaxine overdose, led to conclusion that the positive rapid LFIA test in fact diagnosed the venlafaxine poisoning. The AbuGnost R test detects tramadol with urine cut off values 200ng/ml, but present cross reactivity with O-desmethyl-venlafaxine at cut off values up to 25000ng/ml.

We presented severe VO with self-reported ingested dose of 2250 mg. Most of the cases reported association of fatal outcome with ingested venlafaxine doses in tens of grams as a contrary to the case report of poisoning with 3 grams

venlafaxine with lethal outcome where venlafaxine plasma concentrations were verified by LC-MS/MS (Vignali, Morini, Chen, Stramesi, & Groppi, 2014). The differences in the venlafaxine metabolism is associated with CYP2D6 polymorphism which induce poor, intermediate, extensive and ultrarapid venlafaxine metabolizing phenotypes (Rolla et al., 2014). These facts should be considered when observing poisonings with ingested lower venlafaxine quantities and pay attention to the clinical signs of SS and laboratory findings.

The ingested venlafaxine dose was presented based only on patient's self reporting due to the unavailability of serum venlafaxine quantification, which is a limitations of our analysis. However, the positive data from the interview, the course of clinical presentation, the results from laboratory analysis (hyponatremia), the exclusion of tramadol as the causative agent of poisoning with toxicological analyzes and prolonged patient's cognitive deterioration, were sufficient to confirm the venlafaxine poisoning. Although the clinical presentation of venlafaxine and tramadol as well as their symptomatic treatment overlap to a large extent, the dilemma about absence of clinical improvement when use the antidotal therapy (such as naloxone) in the event of respiratory failure is a key point when treating these two types of poisonings only according to the results of the rapid tests.

4. CONCLUSION

The role of rapid immunoassay test is significant and necessary for the work of the emergency departments, taking in consideration that high concentrations of venlafaxine metabolites induce false positive tramadol immunoassay (AbuGnostRBiognot) test and overlapping clinical presentations. The mandatory principle when making medical decisions should cover synthesis of critically interpreted toxicology analysis, interview data and clinical features of the poisoning, which may help to avoid misleading conclusions and improve the diagnostic and therapy decisions.

REFERENCES

- Abadie, D., Rousseau, V., Logerot, S., Cottin, J., Montastruc, J.-L., & Montastruc, F. (2015). Serotonin Syndrome. *Journal of Clinical Psychopharmacology*, 35(4), 1. <https://doi.org/10.1097/JCP.0000000000000344>
- Allen, K. R. (2006). Interference by venlafaxine ingestion in the detection of tramadol by liquid chromatography linked to tandem mass spectrometry for the screening of illicit drugs in human urine. *Clinical Toxicology (Philadelphia, Pa.)*, 44(2), 147–153. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16615670>
- Bond, G. R., Steele, P. E., & Uges, D. R. A. (2003). Massive venlafaxine overdose resulted in a false positive Abbott AxSYM urine immunoassay for phencyclidine. *Journal of Toxicology. Clinical Toxicology*, 41(7), 999–1002. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/14705849>
- De Picker, L., Van Den Eede, F., Dumont, G., Moorkens, G., & Sabbe, B. G. C. (2014). Antidepressants and the Risk of Hyponatremia: A Class-by-Class Review of Literature. *Psychosomatics*, 55(6), 536–547. <https://doi.org/10.1016/j.psych.2014.01.010>
- Dunkley, E. J. C., Isbister, G. K., Sibbritt, D., Dawson, A. H., & Whyte, I. M. (2003). The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM: Monthly Journal of the Association of Physicians*, 96(9), 635–642. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12925718>
- Fischer, M., Unterecker, S., & Pfuhlmann, B. (2012). Overdose of Venlafaxine with Mild Outcome. *Neuroscience & Medicine*, 3, 327–329. <https://doi.org/10.4236/nm.2012.34038>
- Jha, P., Mazumdar, B., & Bhatt, J. (2006). Analgesic activity of venlafaxine and its interactions with tramadol, celecoxib and amlodipine in mice. *Indian Journal of Pharmacology*, 38(3), 181. <https://doi.org/10.4103/0253-7613.25804>
- Kalra, B., Tayal, V., & Chawla, S. (2008). Antidepressant-like activity of tramadol in mice. *Indian Journal of Psychiatry*, 50(1), 51. <https://doi.org/10.4103/0019-5545.39760>
- Khan, F., Yousef, H., & Errayes, M. (2010). Tramadol toxicity-induced rhabdomyolysis. *Journal of Emergencies, Trauma, and Shock*, 3(4), 421. <https://doi.org/10.4103/0974-2700.70766>
- Melli, G., Chaudhry, V., & Cornblath, D. R. (2005). Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine*, 84(6), 377–385. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16267412>
- Rahimi, H. R., Soltaninejad, K., & Shadnia, S. (2014). Acute tramadol poisoning and its clinical and laboratory findings. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*, 19(9), 855–859. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/25535500>
- Reeves, R. R., & Cox, S. K. (2008). Similar Effects of Tramadol and Venlafaxine in Major Depressive Disorder. *Southern Medical Journal*, 101(2), 193–195. <https://doi.org/10.1097/SMJ.0b013e3181616e66>
- Rolla, R., Gramaglia, C., Dalò, V., Ressico, F., Prosperini, P., Vidali, M., ... Zeppegno, P. (2014). An observational study of Venlafaxine and CYP2D6 in clinical practice. *Clinical Laboratory*, 60(2), 225–231. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/24660534>

- Ryan, N. M., & Isbister, G. K. (2015). Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clinical Toxicology*, 53(6), 545–550. <https://doi.org/10.3109/15563650.2015.1036279>
- Saitman, A., Park, H.-D., & Fitzgerald, R. L. (2014). False-Positive Interferences of Common Urine Drug Screen Immunoassays: A Review. *Journal of Analytical Toxicology*, 38(7), 387–396. <https://doi.org/10.1093/jat/bku075>
- Tashakori, A., & Afshari, R. (2010). Tramadol overdose as a cause of serotonin syndrome: a case series. *Clinical Toxicology*, 48(4), 337–341. <https://doi.org/10.3109/15563651003709427>
- Vignali, C., Morini, L., Chen, Y., Stramesi, C., & Groppi, A. (2014). Distribution of venlafaxine and O - desmethylvenlafaxine in a fatal case. *Forensic Science International*, 242, e48–e51. <https://doi.org/10.1016/j.forsciint.2014.07.011>
- Wilson, A. D., Howell, C., & Waring, W. S. (2007). Venlafaxine ingestion is associated with rhabdomyolysis in adults: a case series. *The Journal of Toxicological Sciences*, 32(1), 97–101. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/17327698>