Provided by:	Department of Addictology, 1st Faculty of Medicine, Charles University, and General University Hospital in Prague	Expert supervisor:	Mgr. Roman Gabrhelík, Ph.D., PharmDr. Magdaléna Šustková, Ph.D.
Faculty:	1st Faculty of Medicine	Teachers:	PharmDr. Magdaléna Šustková, Ph.D., Mgr. Roman Gabrhelík, Ph.D.
Valid from:	2014	Attributes:	Addictology
Semester:	n.a.	Title:	**Biomedical Addictology: Special Issues**
Scope, examination:	n.a.		
Points:	n.a.		
e-Credits:	n.a.		
Examination format:	oral or written		
Scope of instruction per academic year:	6 x 90 min + 45 min		
Number of places:	unlimited		
Minimum number of students:	unlimited		
Course status:	currently available		
Language of instruction:	Czech		
Format of instruction:	part-time		
Level:	Ph.D.		
Note:	Prof. PhDr. Michal Miovský, Ph.D.		

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

Annotation

This course builds upon the Introduction to Biomedical Addictology course and extends it to include other areas, such as research methods used in addictology (a general overview is provided, with a focus on specific models of addiction), the basics of pharmacotherapy as an integral part of a comprehensive therapeutic/preventive approach, epidemiology, and clinical trials.

The knowledge, skills, and competences that the students are expected to acquire (see Section 2) should ensure their general theoretical background and resources for the practical use of biomedical research in addictology.

In summary, the students will learn:

a) general addictology-relevant research methods
b) general epidemiological principles
c) the basics of the (pharmacological) treatment of substance addiction
d) general principles of clinical trials

Course objective

The course is intended to familiarise the students with the current practice of biomedical addictology, including the element of research and theoretical and practical training needed for them to pursue their own research projects and gain a critical insight into work in the field.

The course features several areas of focus. One of them is a general overview of the research methods used in the field. Another is an introduction to the basic principles of the epidemiology of addiction. The core principles of clinical trials will follow up on the outline of the fundamental elements of addictology-specific pharmacotherapy.

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

Descriptors
2. Course outcome descriptors: **Knowledge:** The students will be expected to show thorough and wide-ranging knowledge of the characteristics of scientific and research approaches and methods specific to biomedicine, including their categorisation, and the basic theoretical framework reflecting the state-of-the-art knowledge in the field. Such expertise should encompass a general understanding of topical issues surrounding the practical use of these methods in modern biomedical addictology and in interdisciplinary and transdiciplinary research. They will know and understand the possibilities of combining various research designs and the sampling methods and the data collection, processing, analysis, interpretation, and publication methods such designs involve. They should demonstrate both their understanding of these methods and ability to apply them appropriately with respect to specific ethical aspects of qualitative approaches. **Skills:** Using the knowledge and understanding of the theoretical and practical framework of the biomedical approach and methods, the students should be able to address independently various scientific biomedicine-specific issues in both theoretical and practical terms. They should be able to choose and combine suitable research strategies and methods in such a way as to devise a unique research design that can respond appropriately to the research problem. They can correctly define and categorise the problem while proposing and laying down an appropriate procedure to be used to subject it to scientific enquiry or identify mistakes and/or the shortcomings of any previous procedures. They will be able to act independently in applying ethical principles to an actual research procedure and identifying its strengths and weaknesses. While doing so, they should be able to integrate the

knowledge from different disciplines and correctly interpret and evaluate the results of their work.

Competences:

At their level of expertise, the students are able to recognise on their own the basic types of epidemiological problems and devise procedures and methods to investigate such problems. They should be able to use and work with international literature and transpose modern knowledge across different models, as well as applying these to the context of a given research issue while adhering to ethical principles.

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

Literature

6. Textbooks and information sources:

6.1. Required reading:

1. Koob GF (2009). Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology 56(Suppl 1): 18–31.
2. Koob GF, Lloyd GK, Mason BJ(2009) Development of pharmacotherapies for drug addiction: a Rosetta Stone approach. Nat Rev Drug Discov. 8(6): 500–515
3. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F Addiction: beyond dopamine reward circuity. PNAS, (2011) 108 (37):15037-15042
4. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology1999;10:37-48.
5. Hill AB. The Environment and disease: association or causation? Proc R Soc Med 1965;58:295-300.
6. McMichael AJ. Prisoners of the proximate: loosening the constraints on epidemiology in an age of change. Am J Epidemiol 1999;149:887-897.
7. Samet JM. Concepts of time in clinical research. Ann Intern Med 2000;132:37-44.
8. WHO Statistical Information System (WHOSIS). Indicator definitions and metadata, 2010. http://www.who.int/whosis/indicators/WHS10_IndicatorCompendium_20100513.pdf
9. Samet JM, Munoz A. Evolution of the cohort study. Epidemiol Rev 1998;20:1-15.
10. White E, Hunt JR, Casso D. Exposure measurement in cohort studies: the challenges of prospective data collection. Epidemiol Rev 1998;20:43-56.
11. Cordier S, Stewart PA. Exposure assessment. In W. Ahrens, I. Pigeot, ed. Handbook of Epidemiology. Springer: Germany, 2005. pp. 437-462.
12. Savitz DA. Interpreting Epidemiologic Evidence: Strategies for Study Design and

Analysis. Oxford University Press: Oxford, 2003. pp.205-241.

13. Cole P, Morrison AS. Basic issues in population screening for cancer. J Natl Cancer Inst 1980; 64:1263-1272.
14. Patz Jr. EF, Goodman PC, Bepler G. Screening for lung cancer. New Engl J Med 2000; 343:1627-1633.
15. Langmuir AD. The surveillance of communicable diseases of national importance. N Engl J Med. 1963;268:182-92.
16. Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244-265.
17. Samet JM. Epidemiology and policy: the pump handle meets the new millennium. Epidemiol Rev 2000;22:145-54.
18. Lawrence M. Friedman, Curt D. Furberg, David L. DeMets. Fundamentals of Clinical Trials 4th ed. 2010, XVIII, 445 p.

6.2. Recommended further reading:

1. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar23;340:c332
2. Van Spall HG, Toren A, Kiss A, Fowler RA (March 2007). "Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review". JAMA 297 (11): 1233–40. doi:10.1001/jama.297.11.1233
3. The Lancet (2009). "Phase 0 trials: A platform for drug development?". The Lancet 374 (9685): 176–118. doi:10.1016/S0140-6736(09)61309-X
4. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, 3rd Ed. Lippincott Williams & Wilkins:
5. Baltimore, 2008.

6. Savitz DA. Interpreting Epidemiologic Evidence: Strategies for Study Design and Analysis. Oxford
7. University Press: Oxford, 2003. pp. 163-204.
8. Cordier S, Stewart PA. Exposure assessment. In W. Ahrens, I. Pigeot, eds. Handbook of
9. Epidemiology. Springer: Germany, 2005. pp. 437-462.
10. Bailey, K. R. and Crawley, J. N. (2008). Anxiety-related behaviors in mice. Buccafusco, J. J (Ed.), Methods of behavior analysis in neuroscience, 2nd edition (pp. 77-101). Boca Raton (FL): CRC Press.
11. Barclay, L. L. and Gibson, G. E. (1982). Spontaneous open-field behavior in thiamin-deficient rats. J Nutr. Oct; 112 (10): 1899–905.
12. Bardo, M.T. and Bevins., R.A. (2000). Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology 153:1; 31–43.
13. Beach, H. D. (1957). Morphine addiction in rats. Canadian Journal of Psychology/Revue canadienne de psychologie. Vol 11(2). Jun. 104-112.
14. Becker, H. C., Lopez, M. F., Doremus-Fitzwater T. L. (2011). Effects of stress on alcohol drinking: a review of animal studies. Psychopharmacology (Berl). 2011 November ; 218(1): 131–156.
15. Bozarth, M. A. (1987). Conditioned place preference: a parametric analysis using systemic heroin injections. In Bozarth, M. A. (Ed.) Methods of assessing the reinforcing properties of abused drugs. (pp. 241-273). New York, Springer,
16. Burke, A. R., Forster, G. L., Novick, A. M., Roberts, C. L., Watt, M. W. (2013). Effects of adolescent social defeat on adult amphetamineinduced locomotion and corticoaccumbal dopamine release in male rats Neuropharmacology. April ; 67C: 359–369.
17. Carter, L. P. and Griffiths, R. R. (2009). Principles of laboratory assessment of drug abuse liability and implications for clinical development Drug Alcohol Depend.

December 1; 105S1: S14 – S25.

18. Chefer, V. I., Thompson, A. C., Zapata, A., Shippenberg, T. S. (2009). Overview of brain microdialysis. Curr. Protoc. Neurosci. April ; Chapter: Unit7.1.
19. Cruz, F. C., Quadros, I. M., Hogenelst, K., Planeta, C. S., Miczek, K. A. (2011). Social defeat stress in rats: Escalation of cocaine and "speedball" binge self-administration, but not heroin. Psychopharmacology (Berl). May; 215(1): 165–175.
20. Curzon , P., Zhang, M., Radek, R. J., Fox, G. B. (2008). The behavioral assessment of sensorimotor processes in the mouse: acoustic startle, sensory gating, locomotor activity, rotarod, and beam walking. Buccafusco, J. J (Ed.), Methods of Behavior Analysis in Neuroscience, 2nd edition (pp. 145-177). Boca Raton (FL): CRC Press.
21. Darvesh, A. S., Carroll, R. T., Geldenhuys, W. J., Gudelsky, G. A., Klein, J., Meshul, C. K., Schyl C. J. (2011). In vivo brain microdialysis: advances in neuropsychopharmacology and drug discovery. Expert Opin Drug Discov. February ; 6(2): 109–127
22. Donald, A. and Overton, D. A. (1991). A Historical Perspective on Drug Discrimination. In Glennon, R. A., Drug Discrimination: Applications to Drug Abuse Research.(pp. 5-25). U.S. Government printing office.
23. Fišerová, M. (2000). Historie, příčiny a léčení drogových závislostí. Postgraduální medicína; ročník 2; číslo 3; 288 - 298,
24. Fox, R. H. and Histon, S. M. (1958). Bradykinin formation in human skin as a factor in heat vasodilatation. J. Physiol. I42; 2I9-232
25. Gardner, E., L. (2008). Use of animal models to develop antiaddiction medications. Curr Psychiatry Rep. October ; 10(5): 377–384.
26. Glennon, R. A. and Young, R. (2011). An introduction to drug discrimination. In Glennon, R. A., Young, R. (Eds.) Drug Discrimination: Applications to Medicinal Chemistry and Drug Studies, First Edition. (pp. 3-17). Published by John Wiley & Sons, Inc.
27. Hall, C., Ballachey, E. L. (1932). A study of the rat's behavior in a field. A contribution

to method in comparative psychology. University of California Publications in Psychology, Vol 6, 1932, 1–12.

28. Howell, L. L., Fantegrossi, W. E. (2008). Intravenous drug self-administration in nonhuman primates. In Buccafusco, J. J. (Ed.), Methods of behavior analysis in neuroscience, 2nd edition (pp. 179-198). Boca Raton (FL): CRC Press.
29. Kelemen, E. and Pašťalková, E. (2000). O studiu paměti u lidí a zvířat. Vesmír. Listopad; 633-635.
30. Koob, G. F., Caine, S. B., Roberts, A. J., Parsons, L. H. (2007). Drug self-administration and microdialysis in rodents. In Crawley, J. (Ed.) What's wrong with my mouse? Strategies for rodent behavior phenotyping. (pp. 35-54). San Diego, CA: Society for Neuroscience.
31. Kudrle, S. (2003). Úvod do bio-psycho-sociálního modelu závislosti. In K. Kalina (Ed.), Drogy a drogové závislosti: Mezioborový přístup 1 (pp. 83–89). Praha: Úřad vlády České republiky.
32. Liu, Y., Foll, B. L., Liu, Y., Wang, X., Lu, L. (2008). Conditioned place preference induced by licit drugs: establishment, extinction, and reinstatement. The Scientific World Journal, 8, 1228–1245
33. Lynch, W. J., Nicholson, K. L., Dance, M. E., Morgan, R. W., Foley, P. L. (2010). Animal models of substance abuse and addiction: implications for science, animal welfare, and society. Comp Med. Jun; 60(3): 177–188.
34. Mahler, S. V., Moorman, D. E., Feltenstein, M. W., Cox, B. M., Ogburn, K. B., Bachar, M., McGonigal, J. T., Ghee, S. M., See, R. E. (2013) A rodent "self-report" measure of methamphetamine craving? Rat ultrasonic vocalizations during methamphetamine self-administration, extinction, and reinstatement. Behav Brain Res. Jan 1;236(1):78-89.
35. Maier, E. Y., Abdalla, M., Ahrens, A. M., Schallert, T., Duvauchelle, C. L. (2012) The missing variable: ultrasonic vocalizations reveal hidden sensitization and tolerance-

like effects during long-term cocaine administration. Psychopharmacology (Berl). Feb;219(4):1141-52. (Maier et al., 2012)

36. Mello, N. K. and Negus, S. S. (1996). Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology. Jun; 14(6): 375-424.
37. Miczek, K. A. and O'Donnell, J. M. (1978). Intruder-evoked aggression in isolated and nonisolated mice: effects of psychomotor stimulants and L-dopa. Psychopharmacology (Berl). Apr 14; 57(1): 47-55.
38. Montgomery, K. C. (1955). The relation between fear induced by novel stimulation and exploratory drive. Journal of Comparative and Physiological Psychology, Vol 48(4), Aug, 254-260.
39. Morris, R. G. M. (1981). Spatial localization does not require the presence of local cues. Learning and Motivation. 12; 239-260
40. Mravčík, V., Chomynová, P., Grohmannová, K., Nečas, V., Grolmusová, L., Kiššová, L., Nechanská, B., Sopko, B., Fidesová, H., Vopravil, J., Jurystová, L. (2013) Výroční zpráva o stavu ve věcech drog v České republice v roce 2012 [Annual Report on Drug Situation 2012 – Czech Republic] MRAVČÍK, V (Ed.). Praha: Úřad vlády České republiky.
41. Panlilio, L. V. and Goldberg, S. R. (2007). Self-administration of drugs in animals and humans as a model and an investigative tool. Addiction. December ; 102(12): 1863–1870.
42. Pechnick, R. N., Glasner-Edwards, S., Hrymoc, M., Wilkins, J.N. (2007). Preclinical development and clinical implementation of treatments for substance abuse disorders. Focus; 5: 151-162.
43. Pellow, S., Chopin, P., File, S. E., Briley, M. (1985). Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods. Aug; 14 (3): 149-67.

44. Planeta, C. S. (2013). Animal models of alcohol and drug dependence. Revista Brasileira de Psiquiatria. 35: 140-S146
45. Prus, A. J., James, J. R., Rosecrans, J. A. (2008). Conditioned Place Preference. In Buccafusco, J. J. (Ed.), Methods of Behavior Analysis in Neuroscience, 2nd edition (pp. 59-76). Boca Raton (FL): CRC Press.
46. Sadananda, M., Natusch, C., Karrenbauer, B., Schwarting, R. K. (2012) 50-kHz calls in rats: effects of MDMA and the 5-HT(1A) receptor agonist 8-OH-DPAT. Pharmacol Biochem Behav. 2012 Apr;101(2):258-64
47. Schramm-Sapyta, N. L., Walker, Q. D., Caster, J. M., Levin, E. D., Kuhn, C. M. (2009). Are adolescents more vulnerable to drug addiction than adults? Evidence from animal models. Psychopharmacology (Berl). Sep; 206(1): 1-21.
48. Spragg, S. D. S. (1940. Morphine addiction in chimpanzees. Comparative Psychology Monographs, Vol 15, 7. 132.
49. Stolerman, I. P., Childs, E., Ford, M. M., Grant, K. A. (2011). The role of training dose in drug discrimination: a review. Behav Pharmacol. September ; 22(5-6): 415–429.
50. Thompson, T. and Schuster, C. R. (1964). Morphine self-administration , food-reinforced and avoidance behaviors in rhesus monkeys. Psychopharmacologia. Jan; 7; 5: 87-94.
51. Torregrossa, M. M., Kalivas, P. W. (2008). Microdialysis and the neurochemistry of addiction. Pharmacol Biochem Behav. August; 90(2): 261–272.
52. Vaculín, Š. (2000). Etické a právní aspekty použití zvířat k experimentální práci, Cesk fyziol 49(1), 30-33.
53. Vorhees, C. V. and Williams, M. T. (2006). Morris water maze: procedures for assessing spatial and related forms of learning and memory. Nat Protoc. 1(2): 848–858.
54. Walf, A. A. and Frye C. A. (2007). The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. Nat Protoc. 2(2): 322–328.

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

55. Weeks, J. R. (1962). Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats. Science. Oct 12;138(3537):143-4.
56. Williams, A. M., Reis, D. J., Powell, A. S., Neira, L. J., Nealey, K. A., Ziegler, C. E., Kloss, N. D., Bilimoria, J. L., Smith, C. E., Walker, B. M. (2012) The effect of intermittent alcohol vapor or pulsatile heroin on somatic and negative affective indices during spontaneous withdrawal in Wistar rats. Psychopharmacology (Berl). Sep;223(1):75-88.
57. Young, R. (2009). Drug Discrimination. In Buccafusco, J. J. (Ed.), Methods of Behavior Analysis in Neuroscience, 2nd edition (pp. 39-58). Boca Raton (FL): CRC Press.
58. Zaostřeno na drogy 8/2013. 1-2. Úřad vlády ČR

Methods of instruction
3. Organisation and structure of the course in the part-time format: **Lectures with discussion:** The course is organised as blocks of lessons taking place at times as agreed. Participation in the session is compulsory. Attendance is recorded and included in the final evaluation. Instruction will be provided in three blocks, each lasting three hours (4 x 45-minute lessons). **Homework and extended supporting study materials:** The syllabus includes: a) additional recommended reading, b) additional e-learning support, c) homework assignments and recommendations for home-based studying. **Extended office hours:** In order to facilitate students' homework, the teachers are available for consultations via his/her e-mail and on-line chat for a two-hour period (in the form of consultation) at a time agreed with the students at the session. The date will fall within the credit week.

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

Examination requirements
Course completion requirements: 80% attendance is required. Upon prior agreement with the teacher, illness or other reasons for authorised absence from the session can be compensated for by an individual home-prepared project addressing a relevant topic. **Course passing requirements:** a) 20% of evaluation: attendance (80%) b) 30% of evaluation: activity during lessons + success in test c) 50% of evaluation (examination): final test in basic terms and concepts **Final evaluation:** a) 100-85%: Excellent b) 84-70%: Very good c) 69-55%: Good d) 54% or less: Failed

Syllabus

Thematic Block I:

Title and content: **Research methods in addictology**

The students will acquire a general background to the major research approaches, levels, and methods employed in addictology, with an emphasis on more specific methods, including common experimental models of addiction.

In recent years the study of addiction has been underpinned by the so-called bio-psycho-socio-spiritual model, which reflects, or highlights, the multifaceted nature of the issue. This is also one of the reasons why in the Czech Republic addictology has been defined as a standalone transdisciplinary field of study to integrate all these perspectives into a single domain. Accordingly, addictological research is also very comprehensive and multifaceted in its nature.

The scientific enquiry into the abuse of (psychotropic, narcotic, etc.) substances and addictive behaviour (including substance addiction) involves practically all levels of research, i.e. pre-clinical and clinical research featuring a wide range of investigational approaches, from preparatory phases taking place separately from the organism, such as syntheses of substances, including potential medicinal agents, and binding studies (the testing of substances in terms of their abilities to influence binding sites/receptors), i.e. the (sub-)molecular level (*in vitro*) and research into tissues/tissue cultures and entire organs (*in situ* methods) to methods involving the entire organism (*in vivo*) (in organisms that are either alert and freely moving or anaesthetised). State-of-the-art research at all levels has been using cutting-edge instrumentation and automated testing/computerised data collection and evaluation, which helps in standardising and objectivising the research techniques (making them more independent of the researcher=investigator). In addition, the correct statistical assessment of the data is crucial for any research.

Some general research rules will be mentioned. They include: standard/defined testing

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

conditions (= providing for the reproducibility of results), use of control/standard (exposed to standard factors) individuals for the comparison of effects, and the rules ensuing from statistical data processing, which predicts the validity and utilisation of the results and relevant conclusions.

Pre-clinical experimental research methods generally involve the use of laboratory animals (the most commonly used species and the principles guiding the choice of experimental animals will be mentioned). Animal testing plays a significant role in the understanding of both the biological and environmental factors which are involved in the development of substance addiction. Animal experimentation makes it possible to create specific conditions and model situations where changes can be looked for with respect to selected elements only, which is hardly feasible in human studies. Recent addiction research has used a number of specific experimental animal models of drug addiction designed to examine various stages of the addiction process (including the initiation of substance use, recreational use, the loss of control over usage, drug withdrawal syndrome, and relapse) and factors which affect liability to the development of addiction. Besides the above-mentioned ethical principles, experimental research is governed by a number of additional general rules of major importance. Both experiments on animals and their husbandry when the experiments are not under way must take place in an accredited standard setting (an accredited menagerie and test rooms for experiments on the whole animal) and under standard conditions as defined by the law (in the Czech Republic Act No. 246/1992 Coll. on the protection of animals against cruelty is the relevant legal regulation in this respect). These include a standard room temperature and humidity, sufficient soundproofing, and the observance of a lighting regime (mostly set at 12-hour cycles). The persons who come into contact with laboratory animals (both attendants and researchers) must be properly qualified and trained for work with laboratory animals (staff accreditation). Furthermore, each experimental study must feature a control animal group (this also applies to molecular and other types of both pre-clinical and clinical research). In comparison to the “standard”

reference group (where a well-established agent, a "standard", is applied instead of a new substance under investigation), "control" experimental subjects are exposed to testing conditions and procedures which are totally identical to those applied to "investigational" subjects, but a "placebo/vehicle" is administered instead of a study agent.

Experimental models of addictive behaviour to be covered include: a) drug-conditioned place preference, b) self-administration, c) drug discrimination, and d) low-intensity electrical self-stimulation of selected brain structures. As regards non-specific/general addiction research methods, behavioural methods and microdialysis will be addressed.

In the part dedicated to clinical research, a general outline of methods, including highly sensitive imaging techniques (often used at the preclinical stage), will be provided. Specific aspects of human research will be discussed: its strengths (verbal description, an account of both the current state and the history, including a description of how a person feels about their psychological and emotional state) and weaknesses (inevitable bias – the interplay of too many factors, study groups being too heterogeneous; self-report bias, concealing things, intentional manipulation, inability to express themselves, etc.).

Key terms and concepts:

Comprehensive approach to addiction research. Research – general rules for good research practice – both preclinical and clinical. Division/levels of research, interconnectedness, types of research, methods. Statistics.

Pre-clinical research – experimental animal research – strict rules must be observed, ethics, site and staff accreditation, standardisation, validity, etc.

Choice of pre-clinical methods: methods in general use (such as behavioural methods and microdialysis), (specific) experimental models of addiction – a) conditioned place preference, b) self-administration, c) drug discrimination, d) low-intensity electrical self-stimulation of selected brain structures.

Klinika adiktologie
1. LF UK a VFN v Praze

Choice of clinical methods: including some highly sensitive imaging techniques

Required reading:

1. Mark L. Mitchell , Janina M. Jolley. Research Design Explained Hardcover. Edition: 8th, Cengage Learning. ISBN-13: 978-1133049838

Additional reading:

1. Bailey, K. R. and Crawley, J. N. (2008). Anxiety-related behaviors in mice. Buccafusco, J. J (Ed.), Methods of behavior analysis in neuroscience, 2nd edition (pp. 77-101). Boca Raton (FL): CRC Press.
2. Barclay, L. L. and Gibson, G. E. (1982). Spontaneous open-field behavior in thiamin-deficient rats. J Nutr. Oct; 112 (10): 1899–905.
3. Bardo, M.T. and Bevins., R.A. (2000). Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology 153:1; 31–43.
4. Beach, H. D. (1957). Morphine addiction in rats. Canadian Journal of Psychology/Revue canadienne de psychologie. Vol 11(2). Jun. 104-112.
5. Becker, H. C., Lopez, M. F., Doremus-Fitzwater T. L. (2011). Effects of stress on alcohol drinking: a review of animal studies. Psychopharmacology (Berl). 2011 November ; 218(1): 131–156.
6. Bozarth, M. A. (1987). Conditioned place preference: a parametric analysis using systemic heroin injections. In Bozarth, M. A. (Ed.) Methods of assessing the reinforcing properties of abused drugs. (pp. 241-273). New York, Springer,
7. Burke, A. R., Forster, G. L., Novick, A. M., Roberts, C. L., Watt, M. W. (2013). Effects of adolescent social defeat on adult amphetamineinduced locomotion and corticoaccumbal dopamine release in male rats Neuropharmacology. April ; 67C: 359–369.
8. Carter, L. P. and Griffiths, R. R. (2009). Principles of laboratory assessment of drug abuse liability and implications for clinical development Drug Alcohol Depend. December 1; 105S1: S14 – S25.
9. Chefer, V. I., Thompson, A. C., Zapata, A., Shippenberg, T. S. (2009). Overview of brain

microdialysis. Curr. Protoc. Neurosci. April ; Chapter: Unit7.1.

10. Cruz, F. C., Quadros, I. M., Hogenelst, K., Planeta, C. S., Miczek, K. A. (2011). Social defeat stress in rats: Escalation of cocaine and “speedball” binge self-administration, but not heroin. Psychopharmacology (Berl). May; 215(1): 165–175.
11. Curzon , P., Zhang, M., Radek, R. J., Fox, G. B. (2008). The behavioral assessment of sensorimotor processes in the mouse: acoustic startle, sensory gating, locomotor activity, rotarod, and beam walking. Buccafusco, J. J (Ed.), Methods of Behavior Analysis in Neuroscience, 2nd edition (pp. 145-177). Boca Raton (FL): CRC Press.
12. Darvesh, A. S., Carroll, R. T., Geldenhuys, W. J., Gudelsky, G. A., Klein, J., Meshul, C. K., Schyl C. J. (2011). In vivo brain microdialysis: advances in neuropsychopharmacology and drug discovery. Expert Opin Drug Discov. February ; 6(2): 109–127
13. Donald, A. and Overton, D. A. (1991). A Historical Perspective on Drug Discrimination. In Glennon, R. A., Drug Discrimination: Applications to Drug Abuse Research.(pp. 5-25). U.S. Government printing office.
14. Fišerová, M. (2000). Historie, příčiny a léčení drogových závislostí. Postgraduální medicína; ročník 2; číslo 3; 288 - 298,
15. Fox, R. H. and Histon, S. M. (1958). Bradykinin formation in human skin as a factor in heat vasodilatation. J. Physiol. I42; 2I9-232
16. Gardner, E., L. (2008). Use of animal models to develop antiaddiction medications. Curr Psychiatry Rep. October ; 10(5): 377–384.
17. Glennon, R. A. and Young, R. (2011). An introduction to drug discrimination. In Glennon, R. A., Young, R. (Eds.) Drug Discrimination: Applications to Medicinal Chemistry and Drug Studies, First Edition. (pp. 3-17). Published by John Wiley & Sons, Inc.
18. Hall, C., Ballachey, E. L. (1932). A study of the rat's behavior in a field. A contribution to method in comparative psychology. University of California Publications in Psychology, Vol 6, 1932, 1–12.
19. Howell, L. L., Fantegrossi, W. E. (2008). Intravenous drug self-administration in

nonhuman primates. In Buccafusco, J. J. (Ed.), Methods of behavior analysis in neuroscience, 2nd edition (pp. 179-198). Boca Raton (FL): CRC Press.

20. Kelemen, E. and Pašťalková, E. (2000). O studiu paměti u lidí a zvířat. Vesmír. Listopad; 633-635.
21. Koob, G. F., Caine, S. B., Roberts, A. J., Parsons, L. H. (2007). Drug self-administration and microdialysis in rodents. In Crawley, J. (Ed.) What's wrong with my mouse? Strategies for rodent behavior phenotyping. (pp. 35-54). San Diego, CA: Society for Neuroscience.
22. Kudrle, S. (2003). Úvod do bio-psycho-sociálního modelu závislosti. In K. Kalina (Ed.), Drogy a drogové závislosti: Mezioborový přístup 1 (pp. 83–89). Praha: Úřad vlády České republiky.
23. Liu, Y., Foll, B. L., Liu, Y., Wang, X., Lu, L. (2008). Conditioned place preference induced by licit drugs: establishment, extinction, and reinstatement. The Scientific World Journal, 8, 1228–1245
24. Lynch, W. J., Nicholson, K. L., Dance, M. E., Morgan, R. W., Foley, P. L. (2010). Animal models of substance abuse and addiction: implications for science, animal welfare, and society. Comp Med. Jun; 60(3): 177–188.
25. Mahler, S. V., Moorman, D. E., Feltenstein, M. W., Cox, B. M., Ogburn, K. B., Bachar, M., McGonigal, J. T., Ghee, S. M., See, R. E. (2013) A rodent "self-report" measure of methamphetamine craving? Rat ultrasonic vocalizations during methamphetamine self-administration, extinction, and reinstatement. Behav Brain Res. Jan 1;236(1):78-89.
26. Maier, E. Y., Abdalla, M., Ahrens, A. M., Schallert, T., Duvauchelle, C. L. (2012) The missing variable: ultrasonic vocalizations reveal hidden sensitization and tolerance-like effects during long-term cocaine administration. Psychopharmacology (Berl). Feb;219(4):1141-52. (Maier et al., 2012)
27. Mello, N. K. and Negus, S. S. (1996). Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology. Jun; 14(6): 375-424.

28. Miczek, K. A. and O'Donnell, J. M. (1978). Intruder-evoked aggression in isolated and nonisolated mice: effects of psychomotor stimulants and L-dopa. Psychopharmacology (Berl). Apr 14; 57(1): 47-55.
29. Montgomery, K. C. (1955). The relation between fear induced by novel stimulation and exploratory drive. Journal of Comparative and Physiological Psychology, Vol 48(4), Aug, 254-260.
30. Morris, R. G. M. (1981). Spatial localization does not require the presence of local cues. Learning and Motivation. 12; 239-260
31. Mravčík, V., Chomynová, P., Grohmannová, K., Nečas, V., Grolmusová, L., Kiššová, L., Nechanská, B., Sopko, B., Fidesová, H., Vopravil, J., Jurystová, L. (2013) Výroční zpráva o stavu ve věcech drog v České republice v roce 2012 [Annual Report on Drug Situation 2012 – Czech Republic] MRAVČÍK, V (Ed.). Praha: Úřad vlády České republiky.
32. Panlilio, L. V. and Goldberg, S. R. (2007). Self-administration of drugs in animals and humans as a model and an investigative tool. Addiction. December ; 102(12): 1863–1870.
33. Pechnick, R. N., Glasner-Edwards, S., Hrymoc, M., Wilkins, J.N. (2007). Preclinical development and clinical implementation of treatments for substance abuse disorders. Focus; 5: 151-162.
34. Pellow, S., Chopin, P., File, S. E., Briley, M. (1985). Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods. Aug; 14 (3): 149-67.
35. Planeta, C. S. (2013). Animal models of alcohol and drug dependence. Revista Brasileira de Psiquiatria. 35: 140-S146
36. Prus, A. J., James, J. R., Rosecrans, J. A. (2008). Conditioned Place Preference. In Buccafusco, J. J. (Ed.), Methods of Behavior Analysis in Neuroscience, 2nd edition (pp. 59-76). Boca Raton (FL): CRC Press.
37. Sadananda, M., Natusch, C., Karrenbauer, B., Schwarting, R. K. (2012) 50-kHz calls in rats:

effects of MDMA and the 5-HT(1A) receptor agonist 8-OH-DPAT. Pharmacol Biochem Behav. 2012 Apr;101(2):258-64

38. Schramm-Sapyta, N. L., Walker, Q. D., Caster, J. M., Levin, E. D., Kuhn, C. M. (2009). Are adolescents more vulnerable to drug addiction than adults? Evidence from animal models. Psychopharmacology (Berl). Sep; 206(1): 1-21.
39. Spragg, S. D. S. (1940. Morphine addiction in chimpanzees. Comparative Psychology Monographs, Vol 15, 7. 132.
40. Stolerman, I. P., Childs, E., Ford, M. M., Grant, K. A. (2011). The role of training dose in drug discrimination: a review. Behav Pharmacol. September ; 22(5-6): 415–429.
41. Thompson, T. and Schuster, C. R. (1964). Morphine self-administration , food-reinforced and avoidance behaviors in rhesus monkeys. Psychopharmacologia. Jan; 7; 5: 87-94.
42. Torregrossa, M. M., Kalivas, P. W. (2008). Microdialysis and the neurochemistry of addiction. Pharmacol Biochem Behav. August; 90(2): 261–272.
43. Vaculín, Š. (2000). Etické a právní aspekty použití zvířat k experimentální práci, Cesk fyziol 49(1), 30-33.
44. Vorhees, C. V. and Williams, M. T. (2006). Morris water maze: procedures for assessing spatial and related forms of learning and memory. Nat Protoc. 1(2): 848–858.
45. Walf, A. A. and Frye C. A. (2007). The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. Nat Protoc. 2(2): 322–328.
46. Weeks, J. R. (1962). Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats. Science. Oct 12;138(3537):143-4.
47. Williams, A. M., Reis, D. J., Powell, A. S., Neira, L. J., Nealey, K. A., Ziegler, C. E., Kloss, N. D., Bilimoria, J. L., Smith, C. E., Walker, B. M. (2012) The effect of intermittent alcohol vapor or pulsatile heroin on somatic and negative affective indices during spontaneous withdrawal in Wistar rats. Psychopharmacology (Berl). Sep;223(1):75-88.
48. Young, R. (2009). Drug Discrimination. In Buccafusco, J. J. (Ed.), Methods of Behavior Analysis in Neuroscience, 2nd edition (pp. 39-58). Boca Raton (FL): CRC Press.

49. Zaostřeno na drogy 8/2013. 1-2. Úřad vlády ČR

Thematic Block II:

Title and Content: **Basics of the (Pharmacological) Treatment of Substance Addiction**

The students will learn about the basic pharmacotherapeutic procedures, the general principles and mechanisms of pharmacological treatment as a way of influencing the individual stages of addiction and related complications, and the latest developments and promising tendencies in the treatment of addictive behaviour. An emphasis will be placed on the use of recent neurobiological evidence in the pharmacological treatment of drug addiction. The new objectives of pharmaceutical research will also be mentioned.

The findings presented as part of Introduction to Neuroscience, the neural and molecular correlations, imply a notion of a multi-level and comprehensive therapeutic approach to drug addiction (applicable to prevention in many respects) aimed at: a) lowering the reinforcing capacities of a drug (both positive and negative), b) increasing the rewarding capacities of natural sources of reward (enhancing the perception of the reward they involve), c) inhibiting learnt/conditioned associations (e.g. breaking the bond between the conditioned external reinforcement and the drug), d) enhancing motivation to activities not related to the drug, and (e) boosting inhibitory control.

The comprehensive therapeutic approach may also incorporate the pharmacological treatment of drug addiction, which is helpful in responding to intoxication (detoxification in cases of overdoses), managing severe, even life-threatening, withdrawal symptoms (as part of detoxification), reducing craving, and preventing relapse (anti-craving treatment; substitution).

The mechanisms of the effects of addiction therapies can be described as follows: the pharmaceuticals that are currently used in clinical practice a) influence the known specific mechanisms of the effects of drugs – they mostly act on (i) relevant binding receptors as agonists (nicotine, methadone, etc.), partial agonists (buprenorphine, varenicline), and antagonists (naloxone, naltrexone), or have a combined effect (acamprosate), but can also

(ii) influence drug metabolisation (disulphiram). Another possibility is to b) exert an effect on the more general mechanisms of drug addiction described above, which could be useful in treating certain types of addiction. An α2 agonist (clonidine), for example, reduces the stress-related noradrenergic activity during early abstinence. Recent research has explored the possibilities of treating drug addiction on the basis of the action on DA receptors (DA receptor partial agonists – D2 (aripiprazole) or D3, the action on GABAergic signalling (GABAergic neurotransmission modulators), and glutamatergic signalling (AMPA receptor antagonists [topiramate], NMDA receptor antagonists, mGluR metabotropic receptor agonists, mGluR5 receptor antagonists), brain stress system modulators (CRF1 antagonists, dynorphin antagonists, neurokinin receptor-1 antagonists), and c) other mechanisms, such as vaccination (anti-cocaine vaccine). A chapter of its own in the pharmacotherapy of drug addiction belongs to epigenetic approaches, which are, indeed, still in their very infancy.

Key terms and concepts:

Pharmacotherapy, anti-craving treatment, inhibitory control increase

Required reading:

Koob GF (2009). Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology 56(Suppl 1): 18–31.

Koob GF, Lloyd GK, Mason BJ(2009) Development of pharmacotherapies for drug addiction: a Rosetta Stone approach. Nat Rev Drug Discov. 8(6): 500–515

Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F Addiction: beyond dopamine reward circuity. PNAS, (2011) 108 (37):15037-15042

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

Thematic Block III:

Title and content: **Epidemiology and General Principles I**

Key terms and concepts:

The main areas of focus:

- Historical development of epidemiological thinking
- Causal models and disease models in epidemiology
- Population and time
- Nature of exposure and results
- Measurement of epidemiological risk
- Population health indicators

Required reading:

1. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10:37-48.
2. Hill AB. The Environment and disease: association or causation? Proc R Soc Med 1965;58:295-300.
3. McMichael AJ. Prisoners of the proximate: loosening the constraints on epidemiology in an age of change. Am J Epidemiol 1999;149:887-897.
4. Samet JM. Concepts of time in clinical research. Ann Intern Med 2000;132:37-44.
5. WHO Statistical Information System (WHOSIS). Indicator definitions and metadata, 2010. http://www.who.int/whosis/indicators/WHS10_IndicatorCompendium_20100513.pdf

Additional reading:

1. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, 3rd Ed. Lippincott Williams & Wilkins: Baltimore, 2008.
2. Savitz DA. Interpreting Epidemiologic Evidence: Strategies for Study Design and Analysis. Oxford University Press: Oxford, 2003. pp. 163-204.
3. Cordier S, Stewart PA. Exposure assessment. In W. Ahrens, I. Pigeot, eds. Handbook of

Epidemiology. Springer: Germany, 2005. pp. 437-462.

Thematic Block IV:

Title and content: **Epidemiology and Basic Principles II**

Key terms and concepts:

The main areas of focus:

- Cohort studies
- Degrees of association
- Issues related to epidemiological monitoring and population health monitoring
- Screening and diagnostic accuracy
- Surveillance

Required reading:

1. Samet JM, Munoz A. Evolution of the cohort study. Epidemiol Rev 1998;20:1-15.
2. White E, Hunt JR, Casso D. Exposure measurement in cohort studies: the challenges of prospective data collection. Epidemiol Rev 1998;20:43-56.
3. Cordier S, Stewart PA. Exposure assessment. In W. Ahrens, I. Pigeot, ed. Handbook of Epidemiology. Springer: Germany, 2005. pp. 437-462.
4. Savitz DA. Interpreting Epidemiologic Evidence: Strategies for Study Design and Analysis. Oxford University Press: Oxford, 2003. pp.205-241.
5. Cole P, Morrison AS. Basic issues in population screening for cancer. J Natl Cancer Inst 1980; 64:1263-1272.
6. Patz Jr. EF, Goodman PC, Bepler G. Screening for lung cancer. New Engl J Med 2000; 343:1627-1633.
7. Langmuir AD. The surveillance of communicable diseases of national importance. N Engl J Med. 1963;268:182-92.
8. Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244-265.
9. Samet JM. Epidemiology and policy: the pump handle meets the new millennium. Epidemiol Rev 2000;22:145-54.

Additional reading:

1. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, 3rd Ed. Lippincott Williams & Wilkins: Baltimore, 2008.

Thematic Block V:

Title and content: **Clinical Trials I**

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

Key terms and concepts:

The main areas of focus:

- History of clinical trials
- Definition and features of clinical trials
- Randomisation
- Types of clinical trial designs
- Masking treatment
- Outcome selection/surrogates
- Drug development process

Required reading:

1. Lawrence M. Friedman, Curt D. Furberg, David L. DeMets. Fundamentals of Clinical Trials 4th ed. 2010, XVIII, 445 p.

Additional reading:

1. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar23;340:c332
2. Van Spall HG, Toren A, Kiss A, Fowler RA (March 2007). "Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review". JAMA 297 (11): 1233–40. doi:10.1001/jama.297.11.1233
3. The Lancet (2009). "Phase 0 trials: A platform for drug development?". The Lancet 374 (9685): 176–118. doi:10.1016/S0140-6736(09)61309-X

Thematic Block VI:

Title and content: **Clinical Trials II**

Key terms and concepts:

The main areas of focus:

- Generalisability and representativeness
- Ethical issues
- Analysis by treatment assignment
- Sample size for survival outcomes
- Data monitoring issues
- Reporting trials/CONSORT guidelines
- Publication of clinical trial results
- Using evidence from clinical trials in decision making

Required reading:

1. Lawrence M. Friedman, Curt D. Furberg, David L. DeMets. Fundamentals of Clinical Trials 4th ed. 2010, XVIII, 445 p.

Additional reading:

1. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar23;340:c332
2. Van Spall HG, Toren A, Kiss A, Fowler RA (March 2007). "Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review". JAMA 297 (11): 1233–40. doi:10.1001/jama.297.11.1233
3. The Lancet (2009). "Phase 0 trials: A platform for drug development?". The Lancet 374 (9685): 176–118. doi:10.1016/S0140-6736(09)61309-X

Final revision test: The students will have the opportunity to demonstrate their knowledge and understanding of the subject matter dealt with in this course during the final revision test.

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti

Evropský sociální fond
Praha a EU – Investujeme do vaší budoucnosti