CLINICAL PSYCHOPHARMACOLOGY
BIBB 482 SYLLABUS

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4:00 – 5:00 by appointment

Course Description
This course examines the history, rationale, pharmacology and putative mechanism of action of drugs used in the treatment of disorders and diseases of the central nervous system (CNS). Emphasis is placed on neurobiological processes underlying psychopathology and pharmacological intervention. Drugs currently in use as well as new drugs in development will be covered. Strategies, techniques, issues and challenges of clinical psychopharmacological research will be addressed and new approaches to drug discovery will be covered in depth, including the use of pharmacogenomics and proteomics to understand variability in drug response and identify new molecular drug targets. Specific drug classes to be considered include antidpressants, anxiolytics, antipsychotics, narcotic analgesics, sedative hypnotics, and antiepileptic medications. A contrasting theme throughout the course will be the use of drugs as probes to identify neural substrates of behavior.

Course Objectives
The following objectives will be achieved through lectures, analysis of scientific literature, class discussions, large and small group exercises, individual and group presentations, and written assignments.

1. Student will understand the pharmacology and pharmacodynamics of major drug groups used in the treatment of CNS diagnoses, including antidepressants, antipsychotics, anxiolytics, anticonvulsants, and nootrophics.
2. Student will recognize the strengths and weaknesses of a wide range of research methodologies to screen compounds and test the mechanisms of action of drugs.
3. Students will understand the drug development process from target identification to FDA approval and ongoing safety surveillance.
4. Student will appreciate how pharmacological investigation informs the understanding of the underlying pathology of the illness.
5. Student will access, critique, and assimilate evidence from scientific studies as it relates to translational neuroscience and the search for promising targets for psychotropic drugs.
6. Student will share informed opinions about advances and challenges in experimental psychopharmacology.
7. Student will work effectively with peers as part of multidisciplinary teams.

CLASS POLICIES

Prerequisites: Successful completion of BIBB 109, 269, 380 or an equivalent is required for this course. The level of presentation of course material assumes all students have mastered the content

in the prerequisite courses. Texts used in these prerequisite courses will be most helpful for review and as additional resources for this course.

Required Reading: There is no standard text. The class readings are carefully selected from the vast literature available on topics related to psychopharmacology. Assigned journal articles will be available either in the biomedical library or on-line via Penn Library e-journals. Students are encouraged to explore the scientific literature while locating specific assigned articles.

Background Reading:

- *Principles of Neuropsychopharmacolog.* Feldman, Meyer, and Quenzer. Many students will already have this text from participation in Chemistry of the Brain. This text is also on reserve in the biomedical library.
- *Neuropsychopharmacology: The Fifth Generation of Progress*
  Edited by Kenneth L. Davis, Dennis Charney, Joseph T. Coyle, and Charles Nemeroff 2002 American College of Neuropsychopharmacology. This text is on reserve in the biomedical library http://www.acnp.org/Default.aspx?Page=5thGenerationChapters
- Basic and Clinical Pharmacology, 10th Edition. Pertram G Katzung, MD, Ph.D, 2007
  http://proxy.library.upenn.edu:6954/resourceTOC.aspx?resourceID=16

Course Format: This seminar class will meet once a week for three hours. In addition to lectures and class discussions of assigned reading, learning activities will include weekly written assignments, small group work sessions, and group presentations.

Grading: There will be no formal exams in this seminar class. Semester grades will be based on performance in the following:

- **Class participation (required each week)**
- **Weekly written assignments (approximately 5 single–spaced pages)**
- **Group project and presentation**
- **Final (take-home essay ~10 pages)**

This grading scheme provides the opportunity for students to demonstrate mastery of course content in a variety of modalities including formal and informal oral and written assignments as well as interaction with peers in large and small group discussions, projects, and presentations. **Students who attend class and participate fully in relevant and collaborative ways in class discussions and activities will receive higher grades.** Grading is at the discretion of the faculty. Students may petition to have their grade re-evaluated by submitting a written rationale for the change of grade. The faculty will then have the option to increase, decrease or keep the grade the same.

Participation in Class Discussions: Participation in class discussions is required. Students who prepare for and participate fully in relevant and collaborative ways in class discussions and activities will receive higher grades. Most of the important questions about the pathophysiology and treatment of neuropsychiatiric and neurodegenerative disorders do not have answers, thus, uncertainty and speculation will characterize our class discourse. Rigorous preparation of the weekly assignments will provide sufficient background for meaningful contribution to class discussions. If you are having trouble understanding a concept, please raise the issue in class. Chances are your classmates will have similar questions. If you are concerned that you do not

understand the concepts, please schedule an appointment during my office hours prior to the class meeting so that you can be prepared to participate in class discussions.

Weekly Written Assignments: The weekly written assignments (approximately 5 single-spaced pages) are designed as extensions of the classroom learning experiences, as guidance for reading the scientific literature in a meaningful and efficient manner, and as preparation for class discussion. Rigorous preparation of these assignments will assure that you will be prepared to make significant contributions to the class discourse. As the neuroscience background varies greatly, the assignments should be used as a guide to pursue the assignment topics at your individual level of understanding. Weekly written assignments and class participation are graded separately.

Group Projects: Students will work together to develop a presentation and homework assignment on a topic assigned by the faculty. The group project is an opportunity to demonstrate excellence in several areas: collaboration with peers; utilization of an array of scientific resources to discover the specifics of an unfamiliar topic; ability to organize information in a visual manner for presentation; and finally oral presentation skills.

Final Exam: The final exam will be a 10-page take-home research paper on a topic assigned by faculty. **S**tudents who have accumulated a grade of A on all written submissions, class discussions, and group projects will be exempt from the final exam.

Attendance: Regular attendance is essential; absences are discouraged. Contribution to class discussion is of paramount importance in this class. Neuroscience is a rapidly evolving and exciting field and class discussions will cover many results that are hot off the presses. Regular attendance is essential for students to fully assimilate the course material. Much of what we do in class cannot be obtained or replicated outside of class. Each student is expected to have completed and thought critically about the readings and assignments, You must come to class prepared to contribute to class discussions. Students who attend class regularly will receive higher grades. If circumstances - family or personal health issues, family celebrations or gatherings, deaths in the family, car accidents or dysfunction, work conflicts, or interviews for graduate/medical/vet/dental school - cause you to miss classes, I suggest that you withdraw from the course and resume in a semester when you can devote full participation to the course.

Collaboration: You are encouraged to develop knowledge and ideas from a large variety of resources throughout this course. Most scientists get valuable ideas and feedback from conversations with colleagues and collegial conversation is strongly encouraged on all assignments. In addition to discussions with your classmates, you should also contact authors of your papers and faculty members at this university or others involved in the research we are exploring.

Deadlines*:* Assignment deadlines are absolutely FIRM; assignments will not be accepted after the deadline. Sports, other academic commitments, work and social/volunteer activities are unacceptable excuses for late work or extension requests.

Backing Up: A computer crash is devastating, but not an acceptable excuse for late submissions. Get in the habit of backing up your work regularly. You must retain electronic copies of all submitted work until after you have received your course grade for the semester. I strongly recommend that you have a foolproof back-up method for storing and retrieving your coursework.

MAC-PC Compatibility*:* All written submissions and group presentations must be accessible/readable on my Dell PC and the classroom computer. If you submit a file that cannot be read on my Dell PC or the classroom computer system and I have to send it back to you for reformatting, it will be considered late and all deadline penalties will apply. It is unacceptable to submit a powerpoint presentation that cannot be read, in its entirety on a PC.

Citations: In all written and PowerPoint submissions, you must provide complete citations so that the reader has the necessary information to locate your primary sources. Plagiarism is an academic violation with severe consequences. Please do not take risks with citation issues; consult faculty if you are uncertain when citations are necessary. The assigned scientific papers provide excellent examples of proper citation form. Select one form and use it consistently throughout the semester. In addition, the university provides tutorial services in writing research papers and you are encouraged to avail yourself of these resources if you are not comfortable with your skills in this area.

IMPORTANT NOTE: I will communicate with the class through Blackboard email. Communications may include changes or cancellations in class, office hours, meeting rooms or times, and/ or assignments. Please go into your personal profile in Blackboard and confirm that the email address listed is the email you will be reading on a daily basis. The class topics and reading assignments are subject to change with a weeks notice. These changes will be announced in class, posted on BB and confirmed by email.

	SAMPLE SCHEDULE Clinical Psychopharmacology
1	Introduction Overview
2	Antidepressants
3	Antipsychotics
4	Antiepilepsy Drugs
5	Anxyiolytics
6	Drugs for neurodegenerative diseases
7	Cannabinoids
8	Drug Discovery Guest Speaker Dr. Carlo Ballatore
9	Lithium
10	Pain Medication
11	Pharmacogenetics
12	Student Presentations
13	Student Presentations

SAMPLE READING LIST

PART ONE: THE BASICS

Drug Discovery and Development Process – Preclinical Development through Clinical Trials. The role of the Food and Drug Administration, the pharmaceutical/biotechnology industry and the American Medical Association in the drug development process

Drug Development – Required Reading

- **ALL: Talnetant (SB223412), a new drug entity in clinical trials for schizophrenias**
  - Evangelista (2005) Talnetant: GlaxoSmithKline. Curr Opin Investig Drugs Jul;6(7):717-21 ILL jan 06
- **Group 1: Discovery of antagonists for NK-3 receptor**
  - Sarau et al (1997) Nonpeptide tachykinin receptor antagonists: I. Pharmacological and pharmacokinetic characterization of SB 223412, a novel potent and selective neurokinin-3 receptor antagonist. J Pharmacol Exp Ther. Jun;281(3):1303-11.
  - Giardina et al (1999) Discovery of a novel class of selective non-peptide antagonists for the human neurokinin-3 receptor. 2. Identification of (S)-N-(1-phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (SB223412). J Med Chem Mar 25;42(6):1053-65.
- **Group 2: Characterization of the NK-3 receptor**
  - Oh et al (2000) Sexually dimorphic regulation of NK-1 receptor-mediated elecrophysiological responses in vagal primary afferent neurons. J Neurophysiol Jul;84(1):51-6.
  - Sarau et al (2001) Molecular and pharmacological characterization of the murine tachykinin NK(3) receptor. Eur J Pharmacol Feb16;413(2-3):143-50.
- **Group 3: Imaging the NK-3 receptor in vivo**
  - Bennacef et al (2004) Synthesis and biological evaluation of novel fluor and iodo quinoline carboxamides as potential ligands of NK-3 for in vivo imaging studies. Biorg Med Chem Aug 15:12(16):4533-41.
  - Bennacef et al (2004) Lithiation of functionalized fluoroquinolines: synthesis of dihalo-2-phenylquinoline0-4-carboxamides and in vitro evaluation as NK-3 receptor ligands for medical imaging studies. J Org Chem Apr 2; 69(2):2622-5.

Methods in Neuropsychopharmacology I: Pharmacokinetics and Pharmacodynamics
Methods in Neuropsychopharmacology II: Pharmacogenomics

Pharmacogenetics, Pharmacogenomics, Proteomics – Required Reading

- Group 1: Cacabelos (2005) Pharmacogenomics and therapeutic prospects in Alzheimer's disease. Expert Opin Pharmacother Oct; 6(12):1967-87.
- Group 2: Basile et al (2002) Pharmacogenomics in schizophrenia: the quest for individualized therapy. Human Molecular Genetics 11(20:2157.
- Group 3: Gould and Manji (2004) The molecular medicine revolution and psychiatry: bridging the gap between basic neuroscience research and clinical psychiatry. J Clin Psychiatry May65(5):598-604.

- Group 4: Bishop and Ellingrod (2004) Neuropsychiatric pharmacogenetics: moving toward comprehensive understanding of predicting risks and response. Pharmacogenomics Jul;5(5):463-77.
- Group 5: Mancama and Kerwin (2003) Role of Pharmacogenomics in individualizing treatment with SSRIs. CNS Drugs .17(3): 143-151
- Group 6: Crowley et al (2006) Pharmacogenomic evaluation of antidepressant citalopram in the mouse tail suspension test. Neuropsychopharmacology 31(11):2433-42.
- ALL Background reading:
    - About Pharmacogenomics from the Human Genome Project: http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml
    - How will drug development and testing benefit from pharmacogenomics? http://www.ncbi.nlm.nih.gov/About/primer/pharm.html
    - How does variation in human genes lead to variation in drug response? http://www.pharmgkb.org/
    - HapMap http://www.hapmap.org/index.html.en

PART TWO: CURRENT TREATMENT STRAGTEGIES AND NEW DRUGS IN DEVELOPMENT

This section of the course will review currently available treatment strategies, evaluate therapies now in development, and explore the search for new treatment targets. Particular emphasis will be placed on what we have learned about the brain and the disorders through the use of currently available drugs and how those learnings are guiding the development of new therapeutics.

Schizophrenia and Psychotic Disorders: Antipsychotics and anticonvulsants

- New Drugs in Development: Compare GSKs Talnetant and Sanofis Osanetant . See reading list for Drug Development above.
- Gray and Roth (2007) The pipeline and future of drug development in schizophrenia. Mol Psychiatry ahead of pub
- Kamali (2001) Osanetant Sanofi-Synthelabo. Curr Opin Investig Drugs. 2001 Jul;2(7):950-6. Review. ILL

MIDTERM – What happened to Epvanserin, EMR-62218, lloperidone, Org-5222, LAX-101d, Rimonabant, Zatepine? Individualized short paper (5 pages) tracing the demise of candidate compounds. Focus of the paper: "what killed the drug!"

Mood Disorders: Antidepressants, Lithium

- Meeting the Stress Diathesis Hypothesis:
- Group 1: Nielsen (2005) Corticotropin-releasing factor type-1 receptor antagonists: The next class of antidepressants? Life Sci. Aug 22; [Epub ahead of print]
- Group 2: Adell et al (2005) Strategies for producing faster acting antidepressants. Drug Discov Today. Apr 15;10(8):578-85. Review. ILL

Anxiety Disorders: Antianxiety Agents, Sedative-Hypnotics, Antidepressants

- Group 1: Antibiotic yields anxiolytic: Johnstone et al (2003) Modifying quinolone antibiotics yields new anxiolytics. Nature Medicine; Nov 30;10:1038.

- Group 2: Kalkman and Loetcher (2003) GAD(67): the link between the GABA-deficit hypothesis and the dopaminergic- and glutamatergic theories of psychosis. J Neural Transm Jul;110(7):803-12.
- Group 3: Osanetant for anxiety? Kronenburg et al (2005) Randomized, double-blind study of SR142801 (Osanetant). A novel neurokinin-3 (NK3) receptor antagonist in panic disorder with pre- and posttreatment cholecystokinin tetrapeptide (CCK-4) challenges. Pharmacopsychiatry. Jan;38(1):24-9.

Antiepileptics: Utilization for disorders other than epilepsy

- Yathan et al (2002) Third generation anticonvulsants in bipolar disorder: a review of efficacy and summary of clinical recommendations. J Clinical Psychiatry 63(4):275-283.
- Christopoulos (2002) Allosteric binding sites on cell-surface receptors: novel targets for drug discovery. Nature Rev Drug Discovery 1:198-210.

Neurodegenerative Disorders

- Inhibitors of NOS for Alzheimer's disease: Nathan et al (2005) Protection from Alzheiner's-like disease in the mouse by genetic ablation of inducible NOS. Journal of Experimental Medicine 202:
- Van Dam and De Deyn (2006) Drug Discovery in dementia: the role of rodent models. Nature Reviews Drug Discovery 5:956-970
- SiRNA and Huntington's disease: Harper et al (2005) RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. PNAS; 102 (16)5820-5825.
- Caspace inhibitors and amyotrophic lateral sclerosis: Monocycline trials http://www.clinicaltrials.gov/show/NCT00047723

Drugs of Abuse, Cognitive Enhancers: Opiates and Opioids, Stimulants

- Group 1 Modafanil – Randall et al (2005) Cognitive effects of modafinil in student volunteers may depend on IQ. Pharmacol Biochem Behav. 2005 Sep;82(1):133-9.
- Group 2 Ritalin – Singh (2005) Will the "real boy" please behave: dosing dilemmas for parents of boys with ADHD.Am J Bioeth. Summer;5(3):34-47.
- Group 3 Oxycontin – Lotsch (2005) Pharmacokinetic-Pharmacodynamic modeling opioids. J Pain Symptom Manage May 29(5 supl):S90-103. Review.

PART THREE: THE FUTURE

Student Projects