

Psychopharmacology of Longterm Aggression

Look under Violence

Better Stress Section pulsatile secretion

Immune Privilege

Cognitiveceuticals

Drugable targets

Companies

Career Opportunitites

Carpet bombs

Testing – Safety

Testing – Efficacy

Supporting Industries

BIBB 482 CLINICAL PSYCHOPHARMACOLOGY SYLLABUS

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Solomon Labs B28

Required Reading

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 as they locate 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 o 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

Physician's Desk Reference – On reserve in the biomedical library

Resources

Peer Reviewed journals, examples:

CNS Drugs

Pharmacol Reviews

The Pharmacogenomics Journal <http://www.nature.com/tpj/index.html>

Online Brain Atlases

<http://www.med.harvard.edu/AANLIB/home.html>

<http://www.vh.org/adult/provider/anatomy/BrainAnatomy/BrainAnatomy.html>

National Institute of Mental Health <http://www.nimh.nih.gov>

Food Drug Administration <http://www.fda.gov/>

From Test Tube To Patients http://www.fda.gov/fdac/special/newdrug/ndd_toc.html

National Center for Biotechnology Information

<http://www.ncbi.nlm.nih.gov/About/index.html>

World Health Organization <http://www.who.int/whr/2001/en/>

DSM-IV-TR <http://www.behavenet.com/capsules/disorders/dsm4TRclassification.htm>

Clinical Trials <http://www.clinicaltrials.gov/ct>

Pharmaceutical Research and Manufacturers of America <http://www.phrma.org/howeare/>

Gene Review

<http://www.genetests.org/servlet/access?id=8888890&key=aOQUfXxgluiJz&fcn=y&fw=YyT9&filename=/reviewsearch/searchdz.html>

<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd.section.193>

Dear Class,

Check this out a tutorial for the yeast two hybrid system:

http://www.staff.kvl.dk/~dacoj3/resource/yeast_2H.htm

The yeast two-hybrid system for beginners.

All you need to know:

The two-hybrid system is a molecular genetic tool which facilitates the study of protein-protein interactions. If your two proteins interact, then a reporter gene (e.g. *gall-lacZ* - the beta-galactosidase gene) is transcriptionally activated. And you get a colour reaction on specific media. You can use this to (1) study the interaction between two proteins which you expect to interact and/or (2) find proteins (prey) which interact with a protein you have already (bait).

and there is a lot more on the website>>>>>>>>>

Prerequisites

Successful completion of BIBB 109, 269, 380 or an equivalent is required for this course. The level of presentation of course material assumes that 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.

Course Description

This course examines the history, rationale, pharmacology and putative mechanism of action of drugs used in the treatment of psychiatric disorders. 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 antidepressants, anxiolytics, typical and atypical 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, pharmacokinetics, and pharmacodynamics of major drug groups used in the treatment of CNS diagnoses.
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. Students will work effectively with peers as part of a multidisciplinary team

GRADING

Weekly Assignments: There will be ten weekly written assignments. These assignments provide the basis for class discussions; students are expected to participate in class discussion each week. The written submission and oral participation will be evaluated and a weekly grade of A (2 points) or B (1 point) will be awarded each week for a semester total of 10 points. Assignments 1 - 4 and 6 - 9 will be approximately 5 page critiques of journal articles, comparative analyses of drug classes or drugs within classes, or expositions on new chemical entities in development for a specific CNS diagnosis.

Midterm: The fifth assignment, due Feb 20, 2006, will be a 5-10 page midterm on an assigned topic.

Final Exam: The tenth assignment, due April 3, 2006, will be a 10-20 page final paper prepared in support of your symposium project.

Final grade: Grades for the course will be assigned according to the following guidelines:

A+	>10 and discretion of faculty	B	8.3-8.7
A	9.3-10	B-	8.0-8.2
A-	9-9.2	C+	7.8-7.9
B+	8.8-8.9	C	7.3-7.7
		C-	7.0-7.2

Late assignments: Assignments will not be accepted after the due date unless the student has a letter from administration documenting extenuating circumstances.

Grading criteria will be 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.

Student Symposium, April 10 and 17: See Symposium Guidance for details. Attendance is required on April 10 and April 17 – no exceptions. Absence from any portion of the Student Symposium will result in a deduction of 2-4 points from the semester grade. Students will be evaluated by their peers for their collaborative contribution. An unfavorable evaluation by peers will result in point deductions from the final grade.

. IMPORTANT NOTE: I communicate with the class through Blackboard email. Communications may include cancellations of class or office hours, changes in meeting rooms or times, or changes or additions to the assignment. 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. Also be informed that the class topics and reading assignments WILL vary from the syllabus.

CLASS SCHEDULE and READING LIST

PART ONE: THE BASICS

Jan 9 Overview of course.

Jan 23 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 electrophysiological 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-phenylquinoline-4-carboxamides and in vitro evaluation as NK-3 receptor ligands for medical imaging studies. *J Org Chem* Apr 2; 69(2):2622-5.

Jan 30 Methods in Neuropsychopharmacology I: Pharmacokinetics and Pharmacodynamics

Feb 6 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
- 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 STRATEGIES 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.

Feb 13 Schizophrenia and Psychotic Disorders: Antipsychotics and anticonvulsants

- New Drugs in Development: Compare GSKs Talnetant and Sanofis Osanetant . See reading list for Drug Development above.
- Kamali (2001) Osanetant Sanofi-Synthelabo. *Curr Opin Investig Drugs*. 2001 Jul;2(7):950-6. Review. ILL

Feb 20 MIDTERM – What happened to Epravanserin, 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!”

Feb 27 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

March 13 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.

March 20 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.

March 27 Neurodegenerative Disorders

- Inhibitors of NOS for Alzheimer's disease: Nathan et al (2005) Protection from Alzheimer's-like disease in the mouse by genetic ablation of inducible NOS. *Journal of Experimental Medicine* 202:
- 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>

April 3 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 suppl):S90-103. Review.

PART THREE: THE FUTURE

April 10 and April 17 Student Symposia on Challenges to Discovery of Novel Drug Targets for CNS Diagnoses