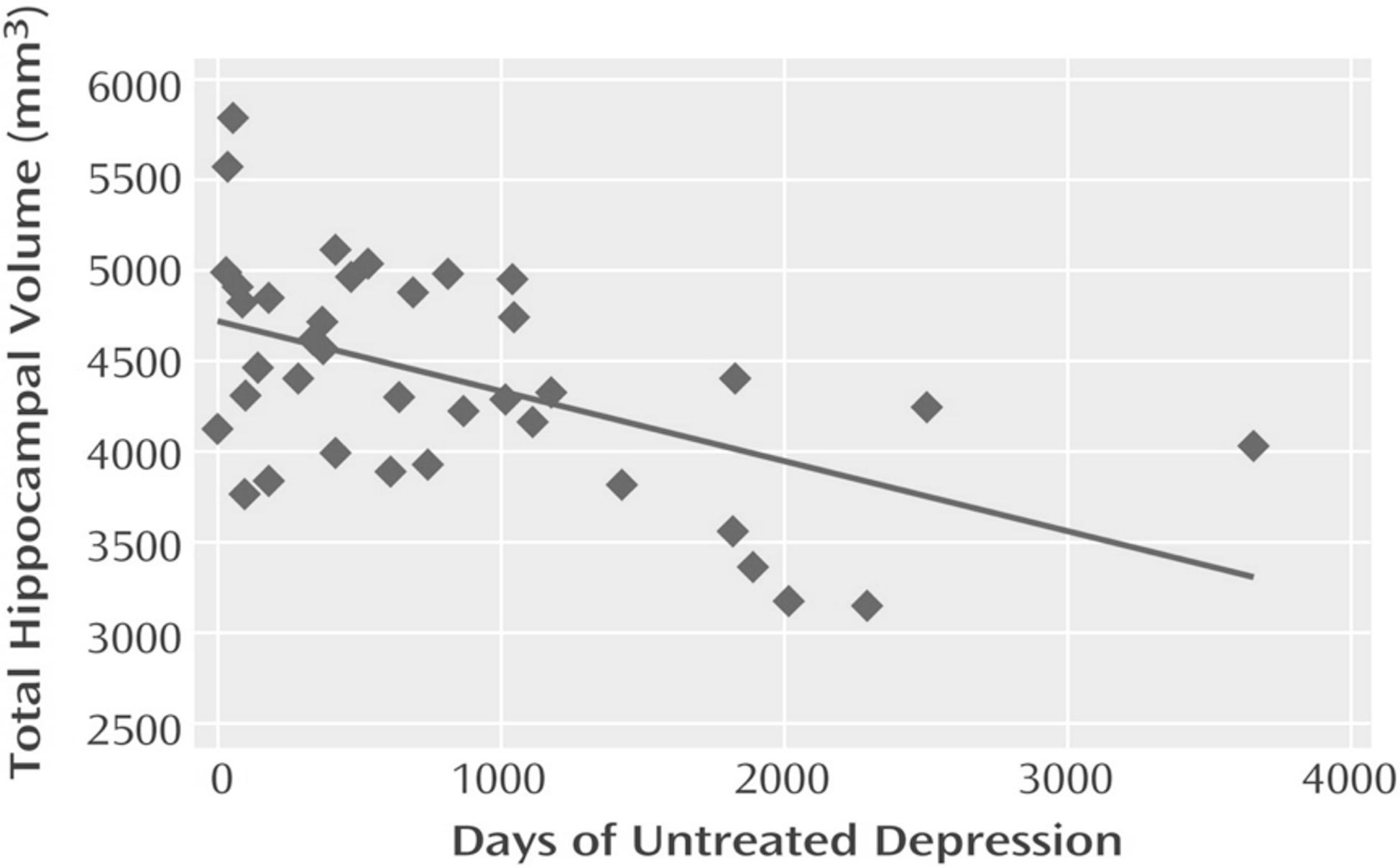
Depression

- Potential causes (genetic predisposition?)
  - *stress-induced* increase in stress hormones like the glucocorticoids
    - interaction with environment (“forced smile” effect)
    - ~50% of depressed patients have an abnormal physiological stress response
  - neurochemical changes in specific regions of the brain
    - deficiencies in NE, DA, 5-HT
    - morphological changes (e.g., shrunken hippocampus)


Total Hippocampal Volume (mm³)
6000
5500
5000
4500
4000
3500
3000
2500
0
1000
2000
3000
4000
Days of Untreated Depression

Depression

- animal tests:
  - learned helplessness / forced swim

The Antidepressants

- Antidepressants also used for:
  - dysthymia
    - anxiety (moving away from the use of *benzodiazepines*)
  - chronic pain
  - sleep disorders
  - migraine headaches
  - nicotine addiction
    - all symptoms (or subtypes) of depression?

Depression

- reduction of "neurotrophic" substances (e.g., BDNF, NGF) in the hippocampus and frontal cortex

    - starts w/ nature and/or nurture-induce deficiencies in "cAMP response element-binding" (CREB) protein
        - nuclear transcription factor for *neurotrophic* substances

            - less CREB production > less BDNF
                - loss of *neuroplasticity* > structural changes (atrophy / loss)
                    - > depression / memory problems

Depression

Depression may be a disorder of neuronal plasticity / survival

- NT deficiencies may be secondary
  - effects of drugs on NTs immediate
    - effects of drugs on symptoms take weeks

The Antidepressants

- Most treatment strategies involve boosting levels of the deficient neurotransmitters
  - prolonging their presence in the synapse
- Interestingly, most therapies ALSO decrease glucocorticoid levels AND increase levels of BDNF and its receptor (trkB)
    - antidepressants
    - placebo
    - physical exercise
    - ECT
    - “talk therapy”
  - All may help to restore plasticity / adaptability to neurons
  - All may also stimulate growth of new neurons (*neurogenesis*)

Depression

Example of how exercise may help:

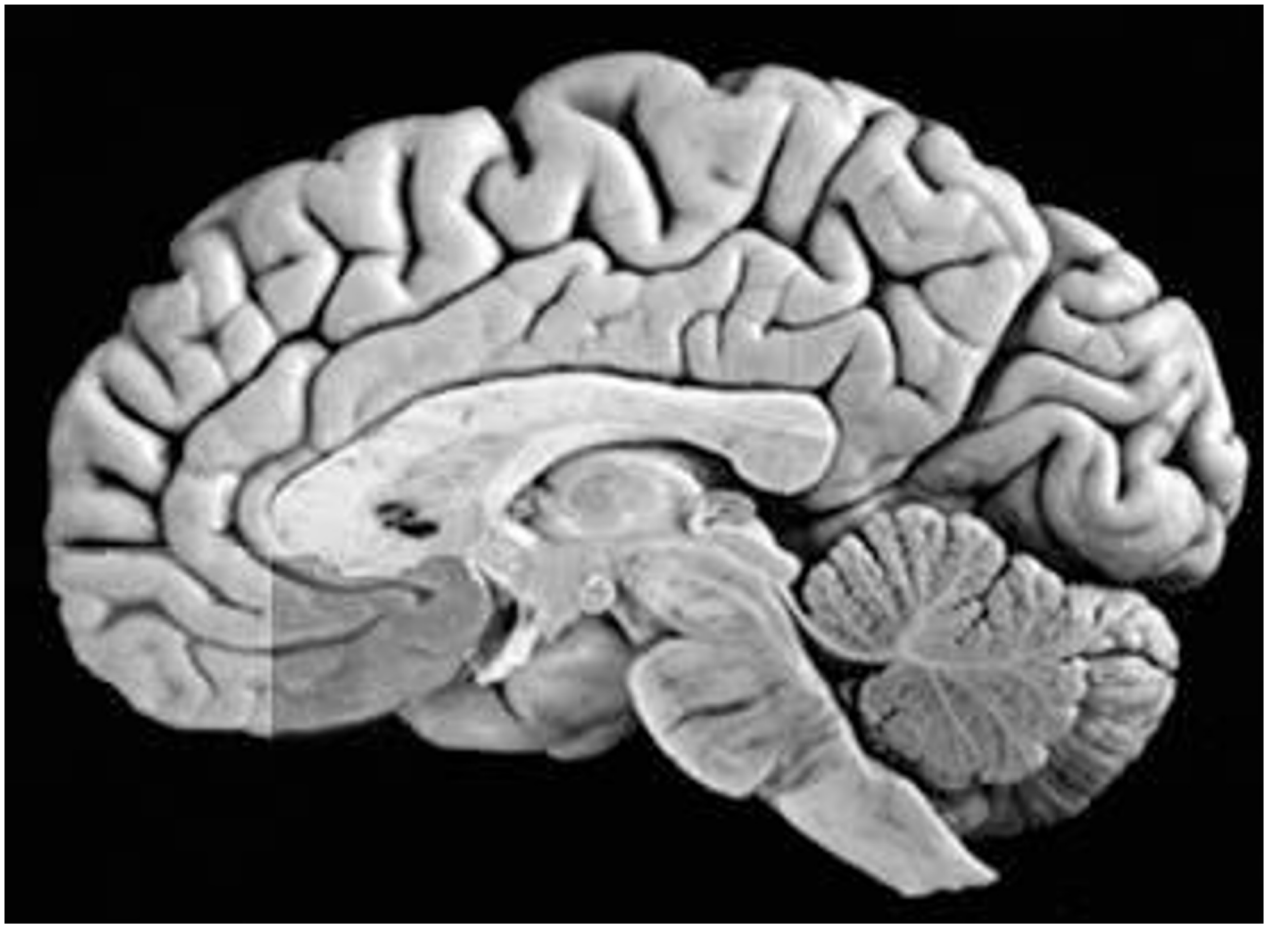
Tryptophan gets turned into serotonin OR (during stress) kynurenine (stimulates inflammatory / immune response)

- kynurenine gets turned into quinolinic acid
- quinolinic acid passes through BBB and causes inflammation

- exercise causes muscles to soak up extra kynurenine

The Antidepressants

- Most treatment strategies ALSO reduce activity levels in the medial prefrontal cortex (mPFC)
  - mPFC hyperactivity is associated with obsessive thoughts

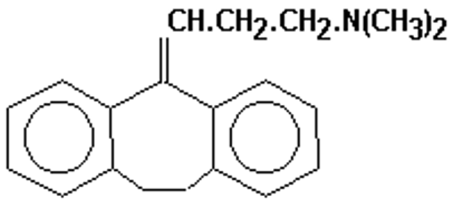


The Antidepressants

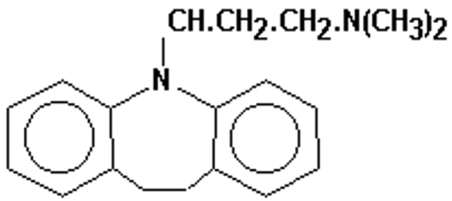
- **“1st Generation” antidepressants**
  - Tricyclics
  - MAOIs (Monoamine Oxidase Inhibitors)
    - both tend to elevate synaptic levels of 5-HT and NE (+)
      - Also, increase BDNF and decrease mPFC activity
- equally effective, but bad (as in fatal) side effects:
  - TCAs – anticholinergic / cardiac toxicity
  - MAOIs – hypertension if taken with certain foods / drugs

The Tricyclic Antidepressants

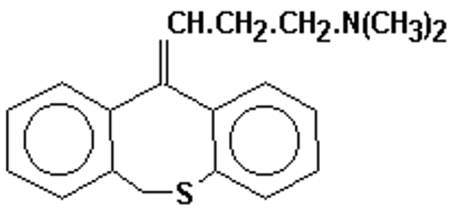
3 ring molecular structure:



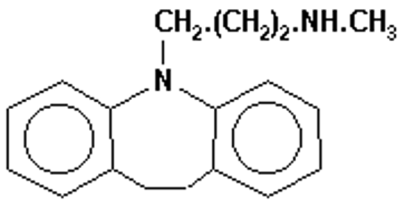
AMITRIPTYLINE



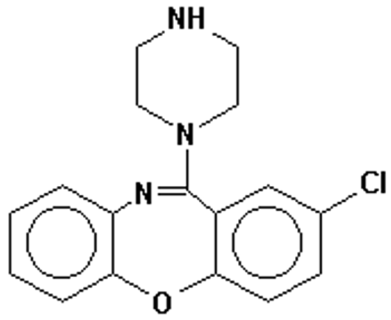
IMIPRAMINE



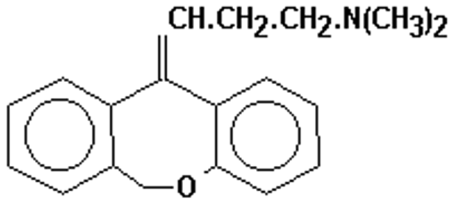
DOTHIEPIN



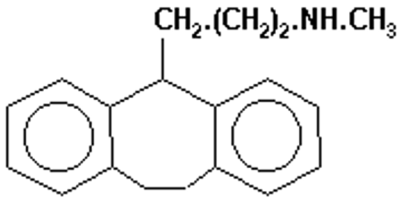
DESIPRAMINE



AMOXAPINE



DOXEPIN



PROTRIPTYLINE

The Tricyclic Antidepressants

- *imipramine* (“Tofranil”) is the archetypical tricyclic antidepressant
  - *amitripyline* (“Elavil”) is another common TCA
  - **all relatively equally effective** – doctors choose based on the particular side effect profile for the individual
- elevate mood / anxiolysis
  - no euphoria / no abuse potential
  - improved physical activity / appetite / sleep patterns
  - analgesic - migraine headaches / chronic pain
  - **Pharmacokinetics -** metabolized in liver (some have active metabolites)
    - long half-lives (taken at bed-time) / longer in elderly

The Tricyclic Antidepressants

Pharmacodynamics:

- 5 main synaptic effects:
  - block **pre**synaptic **5HT reuptake** (antidepressant?)
  - block **pre**synaptic **NE reuptake** (antidepressant?)
  - block **post**synaptic **NE** receptors (low blood pressure)
  - block **post**synaptic **histamine** receptors (drowsiness / sedation)
  - block **post**synaptic **ACh** receptors (confusion, dry mouth, increased heart rate, urinary retention, memory)
- cognitive side effects often counteracted by positive effects (and vice-versa)
  - some side effects (drowsiness) are used in treatment

The Tricyclic Antidepressants

- 4 types of serotonin receptors affected by TCAs:
  - presynaptic: 5HT reuptake receptor (BLOCKED BY TCAs)
    - Causes synaptic build-up of 5-HT
  - postsynaptic: 5HT1, 5HT2, 5HT3 (ACTIVATED BY SEROTONIN IN THE SYNAPSE)

- Known effects of activity at postsynaptic 5-HT receptors:
  - 5-HT_1 (metabotropic):
    - antidepressant / anxiolytic effects
      - Increased CREB > increased neurotrophic substances > increased plasticity
        - Takes several weeks
  - 5-HT_2 (metabotropic):
    - insomnia, anxiety, sexual dysfunction, “5-HT syndrome”
      - $5HT_2$ <u>antagonists</u> ?
  - 5-HT_3 (ionotropic):
    - Nausea
      - antagonists may be good anti-nausea drugs

The Tricyclic Antidepressants

- **Problems:**
  - slow onset of action – days to weeks
  - sometimes associated w/ “emotional numbness”
  - bad side effects – but tolerance often develops
  - heart toxicity in overdose (cardiac depression / arrhythmia)
  - low libido (can become source of marital stress)
- no real withdrawal issues

The Monoamine Oxidase Inhibitors (MAOIs)

the enzyme *monoamine oxidase* (MAO) breaks down and regulate levels of neurotransmitters and other molecules inside axon terminals

- *aminergic* NTs (5-HT / NE / DA) and amino acids like *tyramine*
  - inhibiting these enzymes increases the levels of these molecules in the terminal

- PROBLEM: Fatal hypertension with foods / drugs:
  - Tyramine (fermentation byproduct) – cheese / wine / beer
  - Drugs containing epinephrine-like substances
  - cold medicine, nasal spray, asthma inhalers
- selegine ("Eldapril") - Skin patch devoid of these interactions
- Good for:
  - patients that don't respond to TCAs and SSRIs
  - "atypical" depression: anxiety, panic, eating disorders, bipolar

2nd Generation / Atypical Antidepressants

- Goal of pharmaceutical industry is to develop more effective drugs with fewer side effects
  - Tweak molecules to get more specific pharmacodynamics
  - “Atypical” antidepressants are mostly modifications of the basic TCA chemical structure
- about as effective as the TCAs / MAOIs, with fewer (but still significant) side effects

2nd Generation / Atypical Antidepressants

- Some inhibit 5-HT reuptake AND block 5-HT_2 receptors (*trazodone* "Desyrel" and *nefazodone*) – counteracts side effects of too much 5-HT

- others are better inhibitors of 5-HT and NE reuptake (*clomipramine* "Anafranil", *venlafaxine* "Effexor", *nefazodone, duloxetine* "Cymbalta")

- others have little or no effect on 5-HT, but inhibit reuptake of DA and (to a lesser degree) NE (*bupropion;* "Wellbutrin, Zyban")

  - used to relieve nicotine addiction, but itself is generally not "rewarding"

  - but may cause anxiety / mania (stimulant-like)

"Selective" Serotonin Reuptake Inhibitors

- Common "first-line" treatment is *fluoxetine* ("Prozac / Serafem")
  - also, *paroxetine* ("Paxil"), *sertraline* ("Zoloft"), *fluvoxamine* ("Luvox"), *citalopram* ("Celexa"), and *escitalopram* ("Lexapro")
- Potent 5-HT reuptake receptor inhibitors, and some also NE reuptake. No anticholinergic / antihistamine side effects, and not fatally toxic with OD
  - Also SNRIs (norepinephrine)
- Used as antidepressants & anxiolytics
- Long half-life, and can inhibit drug-metabolizing enzymes in liver, increasing effects of other drugs (e.g., effects of caffeine can be doubled by Luvox)

“Selective” Serotonin Reuptake Inhibitors

- **Adverse effects:**
  - **5-HT syndrome**: too much 5-HT, disorienting, manic, confused, hallucinations
    - Similar to psychedelics
  - **5-HT withdrawal syndrome**: days to weeks
    - 60% of SSRI patients who withdraw from treatment
      - dizziness, GI problems, fatigue, insomnia, anxiety, depression
      - may be result of too little 5-HT (?)
      - rapidly abate with re-administration
  - low or total lack of libido (~80% of patients)
  - pregnancy issues – withdrawal symptoms in infants
    - mouse studies suggest increased anxiety

St. John's Wort

- ***hypericum perforatum***
  - anxiety, depression, sleep disorders, stress reducer
    - many polyphenol / flavonoid antioxidants – (*naphthodianthrones, flavinoids, xanthones*)
      - some inhibit drug-metabolizing enzymes
      - others increase activity of other enzymes
        - increases likelihood of drug interactions
    - psychoactive ingredients - *hypercin, pseudohypercin, hyperforin*
      - amounts of these ingredients extremely variable in commercial products
        - like coffee
        - on average, half the amount on label

Miscellaneous Newer Antidepressants

- Ketamine:
  - Increases BDNF
  - decreases mPFC activity
  - induces synaptic growth in PFC
- Salivia divinorum
- Psilocybin-containing mushrooms

Antidepressants Summary

- with dosage adjustments, all are equally effective
    - slight individual differences in response to the pharmacokinetics / metabolism (CyP enzymes) produce different effects / side effects
        - genetic testing may allow for a more targeted response
- newer drugs generally have fewer or milder side effects
    - this has beneficial cognitive / subjective effects
- 5-HT (or at least its receptors) is the neurotransmitter most associated with affective state
- antidepressants have rapid / acute effect on NT levels, but slow onset of clinical action (~4-6 weeks)
    - matches time required to restore hippocampal CREB levels and thus neuroplasticity
- **THE MAJORITY OF THEIR BEHAVIORAL EFFECTS MAY BE DUE TO EFFECTS ON INCREASED NEUROPLASTICITY (= “ADAPTABILITY”), LOWERED mPFC ACTIVITY, AND/OR PLACEBO EFFECTS**