**ANTIDEPRESSANTS: SSRIs** (p.7)

15. **Dual-Action "SSRIs"** (cont.)

**duloxetine (Cymbalta)**

has now passed clinical trials and can be prescribed (update to Julien, 10th)

blocks reuptake of NE and 5HT (more complete blockage than seen with venlafaxine/Effexor)

good for reducing both depression and anxiety, and pain

½ life = 12 hours (so once a day dosing is OK)

SEs: nausea; no wt. gain or sexual dysfunction seen yet, no sign. increases in BP noted yet

**milnacipran (Ixel)**

in clinical trials currently

also blocks reuptake of NE and 5HT

so far, in treatment of hospitalized depressed pts., Ixel is equal in efficacy to imipramine (Tofranil) and better than SSRIs

seems to show reductions in depression within 2 weeks of start of dosing

16. **Selective NorEpi Reuptake Inhibitors**

**atomoxetine (Strattera)**

a **SNRI**, available in 2003

**increases release of NE and DA x3** in **prefrontal cortex**, but w/o increasing DA in striatum (basal ganglia) or nucleus accumbens (as do CNS stimulants, incl. methylphenidate)

thus, thought **unlikely to have abuse potential**

for treatment of: **ADHD** in children, teens, and adults

may be as effective as methylphenidate (Ritalin) which increases NE/DA x l.5 in prefrontal cortex

**improves mood, attention, social functioning, motivation, energy, self-perception (more than just an antidepressant)**

## ANTIDEPRESSANTS: SSRIs (p.8)

### 16. Selective NorEpi Selective Reuptake Inhibitors (cont.)

**reboxetine (Vestra, Edronax)**

while atomoxetine (Strattera) was approved for tx of ADHD, reboxetine was approved in 2004 for tx of depression

is also a **SNRI** (**little or no effect on DA, 5HT, ACh or H** so is "completely" devoid of SEs related to these latter 4 NTs)

antidepressant effects are seen **within one week** of starting drug

like atomoxetine, reboxetine also improves mood, social functioning, self-motivation & psychological well-being

it also improves **cognitive functioning & sustained attention**

**SEs:** mild increase in heart rate & BP, dry mouth, sweating, urinary retention (mild "**anticholinergic" effects**)

½ life = 12 hours (can dose once a day)

metabolized by CYP3A4 liver enzyme; **no significant liver enzyme effects** (neither inhibition nor induction)

as usual, need to reduce dose in pt. with liver malfunction or in elderly pt.

used to tx.: depression, SAD, PAs; in atypical schizophrenics as augmenting therapy; with olanxapine (Zyprexa) to reduce weight gain seen with that antipsychotic drug

### 17. Future Antidepressants

**modafinil (Provigil)**

a non-CNS stimulant wake-promoting drug, usually used to treat EDS in narcoleptics (improves alertness, psychological well-Being, concentration and reduces fatigue)

does not produce typical CSN psychostimulant SEs (e.g. agitation, depressed appetite, insomnia, wt. loss); is not addicting

may be helpful as augmenting drug to use with antidepressants

**ANTIDEPRESSANTS: SSRIs** (p.9)

17. **Future Antidepressants** (cont.)

**Serotonin 5-HT1 Agonists**

Note: buspirone (BuSpar) is an anxiolytic drug via weak stimulation of 5-HT1A RSs

stimulation of the 5-HT1 RS also results in antidepressant effects (e.g. mirtazapine/Remeron)

e.g. the anxiolytic gepirone (currently in clinical trials)

**Substance P Antagonists (SPAs)**

A new class of antidepressants (and anxiolytics)

Substance P known to be involved in asthma, inflammatory bowel disease (= IBS, irritable bowel syndrome), emesis (vomiting), psoriasis (skin disorder), and pain syndromes (e.g. fibromyalgia, migraine headache)

Substance P is a neuropeptide (or neurokinin), is released in response to stress and to pain (increases perception of both)

attaches to the NK1 RS (neurokinin 1 receptor site)

**SPAs are NK1 antagonists**, which then might decrease pain, stress, and depression

e.g. aprepitant (currently in clinical trials)

**tianeptine** (no brand name yet)

novel new antidepressant that **increases presynaptic reuptake of 5-HT ✍ decreases 5-HT in brain**

May be **neuroprotective against dendritic atrophy** caused by stress

Has been shown to be an **effective antidepressant**

is also helpful in tx of **bipolar disorder, dysthymia, anxiety, & chronic alcoholism**; OK to use in elderly pt.

No adverse SEs related to cognitive, psychomotor, sleep, cardiovas., weight, or sexual effects

**ANTIDEPRESSANTS: SSRIs (p. 10)**
**17. <u>Future Antidepressants</u> (cont.)**

**<u>Dehydroepiandrosterone (DHEA)</u>**

is a **glucocortcoid** hormone (from adrenal cortex)
is a precursor molecule to both estrogen and testosterone
peaks in release at 20-25 years of age, declines by 90% by age 70
sold currently as a "food supplement"
<u>may</u> delay aging process (including cognitive decline), and improve mood; reinforces the idea that (sexual) hormones may have a relationship to depressive symptoms
probably justifiable concern over possibility of masculinizing SEs e.g. acne, male-pattern baldness, increased facial hair, lowering of voice register; and possible liver damage

**<u>S-adenosyl-methionine (SAM, SAMe)</u>**

another substance found in body, involved in metabolic reactions
may have antidepressant effects when given IV (not when given PO) only 1% reaches bloodstream when taken orally
also sold as a "food supplement"
concern over SEs of increased atherosclerosis and coronary artery disease (secondary to increase in homocysteine 2$^{nd}$ to use of this product, assuming the supplement you buy even has any SAM in it!)

**<u>Omega-3 Fatty Acids</u>**

Such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
May have antidepressant effects, esp. as a augmenting drug along with more traditional antidepressants; may be helpful in tx. Of excessive aggression and borderline pts.