- **Asenapine (Saphris)**
  - FDA approved for
    - schizophrenia and bipolar disorder (alone or adjunctive) in adults in 2009 (based on three 6-wk RCTs); 5 bid > 10 bid
    - monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder in pediatric patients aged 10 to 17 years.
  - Pharmacodynamics; in order of decreasing magnitude, blocks
    - ***5HT2C (0.03)***
    - ***5HT2A (0.06)***
    - ***5HT7 (0.13)***
    - ***5HT2B (0.16)***
    - ***5HT6 (0.25)***
    - ***D3 (0.42)***
    - **H1 (1)**
    - **D4 (1.1)**
    - **NE alpha 1a (1.2), NE alpha 2a (1.2), NE alpha 2c**
    - **D2 (1.3)**
    - **D1 (1.4)**
    - **5HT5 (1.6)**
    - **5HT1A (2.5)**
    - **5HT1B (4)**
    - H2 (6.2)
    - Muscarinic (8128)
  - Many similarities chemically to mirtazepine
  - Pharmacokinetics
    - peak in 30-90 minutes
    - half life 24 hours
    - absorption is best sublingually (and when no water/liquid for at least 10 minutes after melts)
    - doesn't work well if swallowed
    - metabolized by 1A2 and direct glucuronidation
    - starting dose 10 mg/d
    - dosing is usually divided bid
    - comes in 5 and 10 mg sublingual rapidly dissolving tabs
    - target dose range:
      - 10 mg/day for schizophrenia
      - 20 mg/day for mania/mixed episodes of bipolar disorder
      - 10 mg/day for mania/mixed episodes of bipolar disorder if also using lithium and valproic acid
  - Onset of improvement in 1 week, but most require 3-6 weeks (and some up to 16-20 weeks).
  - Side effects
    - Somnolence: 9-24% vs.7% with placebo
    - Insomnia 6-16%
    - Muscle side effects (other than akathisia) 6-12%
    - Akathisia 4% with 10 mg/d and 11% with 20 mg/d vs. 3% with placebo
    - Dizziness 3-11%
    - Headache 23%
    - Constipation 4-7%
    - Vomiting 4-7%
    - Lack of sensation in tongue 4-7%
    - Weight gain:
      - as a reported side effect 2% vs. <1% with placebo

- short-term studies: 4.9% gained weight (avg 2.2 lb) vs. 2% with placebo
- long-term: 3.7-14.7% gained weight (avg 2.2 lb) vs. 0.5% with placebo
  - in one study of Saphris vs. Zyprexa:
    - 12% weight gain with Saphris; avg weight gain of 3.52 pounds
    - 29% weight gain with Zyprexa; avg weight gain of 12.32 pounds
- generally occurs early and is not progressive

- Hypertension 2-3%
- Dry tongue 1-3%
- Toothache 3%
- Abnormal taste 3%
- Prolactinemia 2-3%
- Increase in glucose (5-7%) by 3.95 mg/dl
- Increase total cholesterol (8-9%) by 6.53 mg/dl
- Hypertriglyceridemia 13-15%
- QTc prolongation 2-5 msec for dose range 10-40 mg/d

- Efficacy
  - Bipolar disorder
    - Findling, et al, 2015
      - Response rate
        - Saphris 42-54%
        - Placebo 27%
      - Side effects
        - Sleepiness 50%
        - Bad taste in mouth 20-25%
        - Orthostatic hypotension 10-15%
    - 2014-2015
      - 3-week monotherapy trial in 403 pediatric patients (aged 10 to 17 years), of whom 302 patients received Saphris twice daily in doses of either 2.5 mg, 5 mg, or 10 mg.
      - Saphris was shown to demonstrate improvement in Young Mania Rating Scale total score and Clinical Global Impression–Bipolar Severity of Illness overall score vs placebo.
      - The most common side effects of the drug observed in the trial were
        - Sleepiness
        - Dizziness
        - strange sense of taste
        - numbing of the mouth
        - nausea
        - increased appetite
        - feeling tired
        - weight gain.

- Saphris will be available for pediatric patients with bipolar I disorder in 2.5-mg, 5-mg, and 10-mg black cherry–flavored sublingual tablets in the second quarter of 2015.

- Warren et al, 2013; 2 identical, industry sponsored, multicenter, 3-week, DBPC trials; 488 adult patients, with mania or mixed manic episode; Saphris (avg dose 10.8 mg) vs. Zyprexa (avg dose 12.6) vs. placebo
  - Zyprexa>Saprhis>>placebo
- Szegedi et al, 2012; Saphris add on to lithium and/or Depakote, adults
  - Saphris 47.7% response rate vs. 34.4% with placebo; NNT 7.5 at 12 weeks
  - Saphris 43.2% response rate vs. 30.1% with placebo; NNT 7.6 at 12 weeks
- Risperdal and Zyprexa may be more effective for schizophrenia (former) and mania (latter)
  - Mania
    - Response rates
      - Saphris 42.3-42.5%
      - Zyprexa 50-54.7%
      - Placebo 25.2-34%
    - Remission rates
      - Saphris 35.5-40.2%
      - Zyprexa 39.4-46.3%
      - Placebo 22.3-30.9%

- Schizophrenia
  - Short-term
    - Two 6-week double-blind trials (Kane et al; Potkin et al): effective
  - Long-term/relapse prevention
    - 26 week placebo-controlled double blind study:
      - relapse rates
        - 12.1% with Saphris
        - 47.4% with placebo
    - 52 week study, Saphris vs. Zyprexa: some evidence of Zyprexa superiority, some of equivalent efficacy

- Side Effects
  - Somnolence
    - 13-24% vs. 6-7% placebo)
  - Insomnia: 15-16% vs. 13% placebo
  - Muscle/motor:
    - EPS, excldg akathisia: 7-12% vs. 3-7% with placebo
    - Akathisia: 4-11% vs. 2-3% with placebo
  - Decreased sensation in tongue: 6-7% vs. 1% with placebo
  - Glucose: remained mostly normal
  - Lipid levels: remained mostly normal
  - Dizziness: 3-11% vs. 3-4% with placebo
  - QTc changes: minimal (2-5 msec); none with increases >/=60 msec, none with QTc >/= 500 msec total
  - Prolactin levels: no impact vs. some increase
  - Numbness in tongue 6-7% vs. 1% placebo
  - Dry mouth 3% vs. 1% placebo
  - Increased appetite: 0-4% vs. <1% placebo
  - Weight:
    - 2-5% with weight increase vs. 1% placebo
    - 1.1-1.3 kg vs. 0.1-0.2 kg with placebo in short term studies

- In a 52-week study
  - 0-1.7 kg (0 if BMI>27)
  - rate of those with >/=7% increase in body weight: 14.7% (9-22%; 9% if BMI>27)
- Hypersalivation <1-4% vs. 0% placebo
- Stomach upset <1-4% vs. 1% placebo
- Irritability 1-2% vs. <1% placebo
- Anxiety 4% vs. 2% placebo
- White cells reduction has been reported (leukopenia/neutropenia)
- Seizures 0-0.3% (1 of 900+ patients) vs. 0% (of 700+ patients) placebo
- Body temperature regulation issues: rare
- Difficulty swallowing 0-0.2% (1 of 900+ patients) vs. 0% (of 581 patients) placebo; in long term study, occurred in 2/1953 patients on Saphris

◦ 9/2011: 52 cases of hypersensitivity reaction including:
- anaphylaxis
- angioedema
- low blood pressure
- increased heart rate
- swollen tongue
- shortness of breath
- wheezing
- rash