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# ***Bupropion***

- **Wellbutrin IR/SR/XL/Zyban**; Bupropion IR/CR
  - General
    - Developed over 30 years ago, marketed in 1984, and became available in twice-a-day SR in 1998 and once-a-day XL in 2003
    - Approved for the treatment of seasonal major depressive illness with an autumn-winter pattern in 2006 and in 2/08 by Health Canada (equivalent of U.S. FDA)
  - Pharmacology
    - Metabolites (all active)
      - Hydroxybupropion
        - The active metabolite is a more powerful norepinephrine reuptake inhibitor as well as a dopamine reuptake inhibitor
        - peak level of the metabolite hydroxybupropion is 17 times higher than bupropion
        - antidepressant potency is 1/2 that of bupropion
      - Threhydrobupropion—1/5 the antidepressant potency
      - Erythrohydrobupropion—peak level is 7 times higher than bupropion; antidepressant potency is 1/5 that of bupropion
    - Time to peak level:
      - Adults—5 hours with XL; 3 hours with SR; 2 hours in the immediate release form
      - Youth—4.8 hours with XL; 3.4 hours with SR
    - Half-life
      - Adults—21 hours for XL; 10 hours (8-24 hour range) for buproprion immediate release; 20-37 hours for it's active metabolites
      - Youth—significantly shorter half-life so that there is 19-80% more exposure to the active metabolites (primarily and importantly hydroxybuproprion; 16.5 (12-21) hours with XL; 12.1 (9-15.4) hours with SR
    - Strong 2D6 inhibitor (can raise Strattera levels, TCA levels); 2B6 substrate (Prozac and Paxil can raise Wellbutrin levels
    - Common dose ranges
      - 2-7 mg/kg/day in children and adolescents; 150-450 mg/day in adults
      - suggested max
        - 50-250 mg/d in children
        - 350 mg/d in adolescents
        - 450 mg/d in adults
      - under certain circumstances the dose in children may be increased above the maximum dose listed.
  - Mechanism
    - dopamine reuptake inhibition (an order of magnitude less potent than Zoloft) and, less so, serotonin RUI, and, even less so, norepinephrine RUI
  - Some reports of intranasal Wellbutrin abuse (in prison)
  - No evidence of bupropion teratogenicity in experimental animals exposed to high doses and none associated in a small study of women. However, like with other antidepressants, there was a statistically associated increase in the rate of spontaneous abortion (15% versus 4.5-11% in controls), though the role of depression in the rate of spontanenous abortion is not clear.
  - Evidence
    - FDA-approved for adult depression and smoking cessation.
    - Depression
      - Adult
        - Multiple studies demonstrating safety and efficacy
        - Maintenance study, 10 months, 37% recurrence rate vs. 52% placebo
      - Pediatric
        - No controlled studies in pediatric depression
        - Yeghiyan, 2003: demonstrated safety and efficacy of the addition of Wellbutrin SR to other antidepressants in the treatment of refractory depression in adolescents; 23 adolescents;
          - 65% response rate

        - Glod et al, 2003: Wellbutrin SR safe and effective in youths with major depression in open-label trial; 11 adolescents;
            - 73% response rate
        - Daviss et al, 2001: Wellbutrin SR safe and effective in youths with depression (or dysthymia) and ADHD
    - ADHD
        - Adult
            - Wellbutrin XL 300-450 mg in adults: ~55% response rate (defined by 30% or more reduction in symptoms) vs. ~25% with placebo
            - Wellbutrin SR 200 mg twice-a-day in adults: 75% response rate (defined by 30% or more reduction in symptoms) vs. 37% with placebo
            - Most of the symptom relief did not occur until after 5 weeks of therapy
        - Youth
            - Wellbutrin immediate release: 3 controlled studies (Barrickman et al, 1995, Conners et al, 1996, Wilens et al, 2001) in 104 children with ADHD demonstrate safety and efficacy
    - There is also a recent six week open study of demonstrating the safety and efficacy of Wellbutrin in reducing smoking in adolescents (Upadhyaya, 2003).
    - Safe and effective for smoking cessation for which it is roughly twice as effective as placebo and as effective as nicotine replacement (though, for Wellbutrin and nicotine replacement, abstinence rates are still only 19-36%).
- Side effects
    - Weight loss in 14-19% of patients (2-3X more than placebo)
        - appetite suppression
    - Nervousness (13.9%)
        - anxiety (5-6% of patients)
        - activation (3-9% of patients)
        - irritability
            - Wilens, 2005 (adult ADHD): 6% vs. 2% placebo
        - agitation
            - Of 476 patients who took inadvertent extra doses of Wellbutrin (Shepherd, 2005): 8.2%
        - restlessness
    - Dry mouth
        - 9.2-14%
        - Wilens, 2005 (adult ADHD): 12% vs. 5% placebo
    - Nasopharyngitis
        - Wilens, 2005 (adult ADHD): 9% vs. 2% placebo
    - Constipation
        - 8.7%
        - Wilens, 2005 (adult ADHD): 6% vs. 2% placebo
    - Dizziness
        - 7%
        - Wilens, 2005 (adult ADHD): 6% vs. 1% placebo
        - Of 476 patients who took inadvertent extra doses of Wellbutrin (Shepherd, 2005): 7.4%
    - Sweating
        - 7%
    - Ear ringing
        - Wilens, 2005 (adult ADHD): 6% vs. 0% placebo
    - Insomnia
        - 5.3-16%
        - Wilens, 2005 (adult ADHD): 12% vs. 7% placebo
    - Nausea
        - 2-4.0%
        - Wilens, 2005 (adult ADHD): 9% vs. 9% placebo
        - Of 476 patients who took inadvertent extra doses of Wellbutrin (Shepherd, 2005): 6.7%
    - Palpitations
        - 4%
        - Of 476 patients who took inadvertent extra doses of Wellbutrin (Shepherd, 2005): 5.5% with fast heart rate

- Headache
  - 3.5%
  - Wilens, 2005 (adult ADHD): 17% vs. 14% placebo
- Weight gain
  - 2-3% (25-50% less than placebo)
- Sexual dysfunction
  - 1%
  - Can treat sexual side effects of serotonin-specific reuptake inhibitors although case reports of sexual side effects from use of Wellbutrin alone.
- Tremor
  - Of 476 patients who took inadvertent extra doses of Wellbutrin (Shepherd, 2005):7.1%
- Dizziness
- Muscle aches
- Ear ringing
- Drowsiness/fatigue
  - 0.3%
  - Wilens, 2005 (adult ADHD): 8% vs. 11% placebo
  - Of 476 patients who took inadvertent extra doses of Wellbutrin (Shepherd, 2005): 6.1%
- Risk of electroencephalographic abnormalities and seizures.
  - Wellbutrin was in the process of being released in 1984, but it's release was delayed until 1986 pending evaluation of it's risk of inducing seizures: when used at a dose range of 0-600 mg/day in adult non-depressed, women hospitalized due to bulimia nervosa, the rate was 0.8% (37/4,259 patients)
  - It was re-released in 1986 when it became clear that the increased risk was dose-related and tended to occur in specific populations (e.g., clients with bulimia nervosa).
  - Seizures have been documented in doses of less than 450 mg/day, especially when combined with alcohol. drugs, and/or other medications, and especially if sudden discontinuation of alcohol or sedatives
  - Risk of seizure is dose-dependent and increased additively by concurrent use of alcohol, stimulants, or cocaine:
    - Wellbutrin 0-450 mg/day 0.44% (15/3,395 patients)
      - Wellbutrin SR up to 300 mg/day—0.1% (in over 3,000 patients)
      - Wellbutrin IR 300-450 mg/day—0.4% (13/3,200 patients)
      - Wellbutrin IR 100-450 mg/day, 102-site study—0.36%
    - Wellbutrin 450-600 mg 4%
    - 10/05: analyzing 17,586 patient-years of Wellbutrin use in the UK, 22 seizures were reported; ***the relative incidence of seizures in the first 28 days of use is one seizure per 6,219 first-time Wellbutrin users which is comparable to other antidepressants.***
    - Shepherd, 2005: of 476 patients who took inadvertent extra doses of Wellbutrin, 4 (0.8%) developed seizures, one of which developed status epilepticus
    - Intentional overdose of Wellbutrin: 11-15% risk of seizures
- Case reports of delusions, hallucinations, and tics have been reported in children
  - Of 476 patients who took inadvertent extra doses of Wellbutrin (Shepherd, 2005): 0.4%
- Case reports of serum sickness (rash, joint pains, fever, lymph node enlargement)
- Co-administration with lithium, l-dopa, and fluoxetine may increase risks and frequency of side effects.
- Pregnancy
  - No evidence of bupropion teratogenicity in experimental animals exposed to high doses
  - None associated in a small study of women.
  - As with other antidepressants, there was a statistically associated increase in the rate of spontaneous abortion (15% versus 4.5-11% in nonteratogen controls); it is not clear if this is related to depression or treatment
  - GSK registry 2005-2005: increased risk of cardiac malformations
- Case reports of delusions, hallucinations, and tics have been reported in children
  - Of 476 patients who took inadvertent extra doses of Wellbutrin (Shepherd, 2005): 0.4%
- Rash, urticaria and case reports of serum sickness (rash, joint pains, fever, lymph node enlargement)
- Co-administration with lithium, l-dopa, and fluoxetine may increase risks and frequency of side effects.

- A bupropion analogue GW320659 is also being investigated.
- The + enantiomer of the 6-hydroxy metabolite of bupropion is being investigated (as gsk 353162) for safety and efficacy

A Systematic Review of the Use of Bupropion for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

Qin Xiang Ng

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**INTRODUCTION:** Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neuropsychiatric disorders of childhood and adolescence. Stimulants are usually the first choice of drug; however, as many as 20% of patients do not respond to them. Stimulants may also worsen comorbid sleep, mood, and anxiety disorders, and they are associated with problems of misuse and diversion. Bupropion, a dopamine and norepinephrine reuptake inhibitor, is a promising nonstimulant alternative with reports of positive outcomes for ADHD management in both adolescent and adult populations. This study systematically reviews clinical trials on the subject.

**METHODS:** Using the keywords bupropion or Wellbutrin or Zyban or Elontril and attention deficit hyperactivity disorder or ADHD or ADDH, a preliminary search on the PubMed and Ovid databases yielded 25,455 articles published in English between January 1, 1988 and May 1, 2016. Of these, there were only six articles on clinical trials involving children. Full articles were also reviewed for references of interest.

**RESULTS:** All available open, controlled, and randomized trials demonstrated bupropion's efficacy in improving ADHD symptoms. The three head-to-head trials found that bupropion had efficacy comparable to methylphenidate ($p > 0.05$). However, a large double-blind, placebo-controlled multicenter study of bupropion found smaller effect sizes for bupropion, as quantified using teacher and parent ratings of ADHD symptoms, than methylphenidate. In terms of tolerability, a head-to-head trial found that headache was observed more frequently in the methylphenidate-treated group than in the bupropion-treated group, whereas the frequency of other side effects did not differ significantly.

**CONCLUSION:** Current findings should be interpreted with caution because of the very limited database. Bupropion should be considered for pharmacological management of childhood and adolescent ADHD, but more randomized controlled trials with larger sample sizes are warranted. There is also some evidence of its benefits in children with comorbid ADHD and conduct, substance use, or depressive disorders.

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