NOREPINEPHRINE-DOPAMINE REUPTAKE INHIBITOR

Bupropion

Wellbutrin SR, Wellbutrin XL, Aplenzin, Forfivo XL, Zyban, Auvelity

Activating non-serotonergic antidepressant that spares sexual function and weight, but lowers the seizure threshold in a dose-dependent way.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	SEIZURE RISK
300-450 mg/day PO (XL)	21 h; OH-bupropion 20 h	CYP2B6; strong 2D6 inhibitor	0.1% at 300 mg/d; 0.4% at 450

FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk in children, adolescents, and young adults in short-term trials, with no increase in patients aged 65 and older. In patients of all ages started on antidepressant therapy, monitor closely for clinical worsening and emergent suicidal thoughts.

INDICATIONS

- FDA-approved for major depressive disorder in adults in immediate-release, sustained-release, and extended-release formulations.
- FDA-approved as the extended-release tablet for prevention of seasonal affective disorder, started in autumn before symptoms typically begin.
- FDA-approved as Zyban for smoking cessation, begun one to two weeks before the target quit date and continued 7 to 12 weeks.
- Combined with dextromethorphan as Auvelity for major depressive disorder and with naltrexone as Contrave for chronic weight management.
- Off-label for adult ADHD, for antidepressant-induced sexual dysfunction as an add-on, and for augmenting a partially effective SSRI.
- Off-label for methamphetamine use disorder in combination with injectable naltrexone, supported by a randomized multisite trial.

DOSING & TITRATION

- Immediate-release starts at 100 mg twice daily, may go to 100 mg three times daily, with a **150 mg** single-dose cap and 450 mg/day total.
- Sustained-release starts at 150 mg each morning, increases to 150 mg twice daily at least 8 hours apart, with a maximum of **400 mg/day**.
- Extended-release starts at 150 mg each morning and increases to 300 mg each morning after four days, with a maximum of **450 mg/day**.
- Aplenzin uses the hydrobromide salt, where 174, 348, and 522 mg correspond to 150, 300, and 450 mg of bupropion hydrochloride.
- In severe hepatic impairment give no more than **150 mg every other day**; reduce the dose or frequency in renal impairment as well.
- Give the last dose before mid-afternoon to limit insomnia, and taper is generally unnecessary given the absence of a withdrawal syndrome.

MECHANISM OF ACTION

- Inhibits the norepinephrine and dopamine transporters with essentially no effect on serotonin reuptake, which is unique among antidepressants.
- The absence of serotonergic action explains why it does not cause sexual dysfunction, weight gain, or serotonin syndrome.
- Its active metabolite hydroxybupropion contributes substantially to effect and reaches concentrations several times those of the parent drug.
- It is also a noncompetitive nicotinic acetylcholine receptor antagonist, which underlies its efficacy in smoking cessation.
- Dopaminergic and noradrenergic activation lowers the seizure threshold in a concentration-dependent manner, the defining safety limit.

PHARMACOKINETICS

- Rapidly absorbed with extensive first-pass metabolism; food has little effect, though the extended-release shell may appear intact in stool.
- Half-life is about **21 hours** for bupropion and roughly 20 hours for the active metabolite hydroxybupropion.
- CYP2B6 generates hydroxybupropion, so CYP2B6 inducers and inhibitors shift the balance between parent drug and metabolite.
- Bupropion and hydroxybupropion are both potent CYP2D6 inhibitors, which is the drug's single most important interaction property.
- In severe cirrhosis both the parent and metabolite accumulate markedly, requiring dosing no more often than every other day.

ADVERSE EFFECTS

- Insomnia, dry mouth, headache, nausea, tremor, agitation, and anxiety are the most common effects and reflect its activating profile.
- Seizure incidence is about **0.1 percent** at 300 mg/day of the sustained-release form and rises to roughly 0.4 percent at 450 mg/day.
- Weight loss occurs in about 25 percent of patients, and it is essentially free of the sexual dysfunction that limits SSRIs and SNRIs.
- Hypertension can worsen, particularly when combined with nicotine replacement, so blood pressure should be checked during titration.
- Psychosis, mania, and severe agitation can be precipitated, and the risk is highest in undiagnosed bipolar disorder.
- Bupropion causes false-positive amphetamine results on urine immunoassay screening, which requires confirmatory testing.

MONITORING

- Screen at baseline for seizure history, head injury, eating disorder, and any plan to stop alcohol or benzodiazepines abruptly.
- Check blood pressure at baseline and during titration, especially when a nicotine patch or a stimulant is used concurrently.
- Assess suicidality, activation, agitation, and sleep weekly for the first four weeks and after each dose increase.
- Review the medication list for CYP2D6 substrates at initiation and whenever a new drug is added, since inhibition is potent.
- Track response with the PHQ-9 every two to four weeks and reassess the diagnosis if activation increases without mood improvement.

INTERACTIONS & CAUTIONS

- Contraindicated in seizure disorder, in current or prior bulimia or anorexia nervosa, and with abrupt cessation of alcohol or sedatives.
- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Potent CYP2D6 inhibition raises levels of tricyclics, metoprolol, atomoxetine, risperidone, and vortioxetine and blocks tamoxifen activation.
- Additive seizure risk with tramadol, theophylline, systemic steroids, antipsychotics, and stimulants, and with any condition lowering the threshold.
- CYP2B6 inducers such as ritonavir, efavirenz, and carbamazepine substantially reduce bupropion levels and may cause apparent nonresponse.

SPECIAL POPULATIONS

- Pregnancy data are reassuring overall, and bupropion is often continued when it is the only agent that has worked.
- Relative infant dose in breast milk is low, but rare infant seizures have been reported, so monitor the infant if breastfeeding.
- Not approved in pediatrics for depression; adult ADHD data are stronger than pediatric ADHD data, and both uses are off-label.
- In older adults reduce the dose and watch for agitation, insomnia, and hyponatremia, though hyponatremia is rarer than with SSRIs.
- In severe hepatic impairment cap at 150 mg every other day; in renal impairment reduce dose or frequency because metabolites accumulate.

PRESCRIBING PEARLS

- The antidepressant that does not cause sexual dysfunction or weight gain, which drives most of its use.
- Absolutely contraindicated in seizure disorder and in any history of bulimia or anorexia nervosa.
- Potent 2D6 inhibitor: recheck metoprolol, atomoxetine, and tamoxifen whenever you add it.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.