THE PACKAGE INSERT SERIES

Bipolar Medications — What Five Labels Say About the Drugs 6 Million Americans Combine

BY

Unbekoming

8 April 2026

unbekoming.com

Fifty-seven percent. That is the somnolence rate for Seroquel in bipolar depression trials — not drowsiness as a side effect that some patients may experience, but a majority of trial participants sedated on the most prescribed antipsychotic in the United States. The FDA-approved label reports it plainly, in a table, next to the placebo rate of 15%. The drug that millions take daily for bipolar depression puts most of its users to sleep.

That number appears on page 23 of the Seroquel prescribing information. On nearby pages: Depakote's label warns it causes neural tube defects, decreased IQ, and neurodevelopmental disorders in children exposed in utero. Abilify's discloses post-marketing reports of pathological gambling, compulsive sexual urges, and binge eating — urges patients may not recognise as abnormal. Lithium, the oldest drug in this group, carries a 530-line label while the others run to thousands — because it was approved in 1970, before the FDA required the clinical trial data that modern labels demand. And every one of these five drugs admits, in its own mechanism of action section, that how it works "is unknown" or "unclear" or "has not been established". These are statements from the FDA-approved labels, written by the manufacturers, reviewed by the regulators, and filed with the agency.

This installment covers five drugs from three pharmacological families: quetiapine (Seroquel), an atypical antipsychotic; lithium (Lithobid), a lithium salt; lamotrigine (Lamictal) and divalproex sodium (Depakote), both anticonvulsants; and aripiprazole (Abilify), another atypical antipsychotic. Together they represent the most commonly prescribed medications for bipolar disorder in the United States. What makes this class different from statins or ACE inhibitors — the subjects of previous installments — is that bipolar patients routinely take two or three of these drugs simultaneously. Each label was written as if the drug would be used alone or with one specified co-medication. The reality of the prescription pad is something else entirely.

These drugs appear to work because they sedate, flatten and suppress. The labels document this in their own adverse reaction data: 57% somnolence on Seroquel for bipolar depression; 34% somnolence as adjunct therapy for mania; 19% somnolence on Depakote; sedation and akathisia on Abilify. Lithium's discoverer, John Cade, found it by accident in 1949 when guinea pigs injected with lithium became "extremely lethargic and unresponsive to stimuli". He then tried it on hospital inmates and reported a "nonspecific leveling effect". Controlled studies of lithium in normal volunteers, led by NIMH director Lewis Judd, found "a general dulling and blunting of various personality functions". The volunteers' partners and roommates noticed the dulling. The trained mental health professionals evaluating the same volunteers "were unable to detect any behavioral changes". The early neuroleptics were originally called tranquillisers and marketed for their "taming" properties. They were

rebranded as “antipsychotics” and “mood stabilisers” — but the pharmacology did not change with the name. As psychiatrist Peter Gøtzsche has observed, these drugs “don't stabilise anything”. Their primary effect is to suppress emotional responsiveness. A person who has been chemically subdued will score lower on a mania rating scale. That reduction in score is what the trials measured, and what the FDA accepted as evidence of efficacy.

Once started, these drugs are difficult to stop — and the difficulty is built into the pharmacology, not the patient. In 1999, Harvard's Ross Baldessarini reported that half of all patients relapsed within five months of quitting lithium. Without any drug exposure, it took nearly three years for 50% of bipolar patients to relapse naturally. The time between episodes after lithium withdrawal was seven times shorter than the natural course of the illness. In the few studies where patients were gradually withdrawn, only 29% relapsed — a rate lower than the drug-maintained group. What the withdrawal studies actually demonstrated was not that lithium prevented relapse, but that stopping lithium triggered it. Patients who took the drug and then quit ended up, in the words of UK psychiatrist Joanna Moncrieff, “worse than if they had never had any drug treatment”. Scottish psychiatrist Guy Goodwin concluded in 1993 that lithium may be “harmful to bipolar patients” if they take it and then stop within the first two years. Seroquel's label documents a discontinuation syndrome in 12.1% of patients — insomnia, nausea, vomiting, dizziness, irritability — and advises gradual withdrawal. Neither antipsychotic in this group provides a structured taper protocol for bipolar patients.

The Package Insert reads the FDA-approved prescribing information for a major drug class in each installment and reports what the labels say — including what they admit has not been studied. If you're currently taking bipolar medications, considering one, or have a family member on one, this is the installment to start with.

None of Them Know How They Work

Every one of these five labels admits, in its mechanism of action section, that the drug's mechanism is either unknown, unclear or unestablished. Lithium: “the specific biochemical mechanism of lithium action in mania is unknown.” Depakote: “the mechanisms by which valproate exerts its therapeutic effects have not been established.” Seroquel: “The mechanism of action of quetiapine in the listed indications is unclear.” Lamictal delivers a double admission — the anticonvulsant mechanism is unknown, and separately, “The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established.” Abilify: “unclear.”

These drugs were not designed to correct a known biochemical defect. They were approved because patients scored lower on mania rating scales for several weeks in short-term trials, and the FDA considered that sufficient. When a drug's mechanism is unknown, predicting what it does to the body over years becomes a different kind of problem. The metabolic

damage, endocrine disruption and reproductive harm documented later in these labels were not predicted from any mechanism — they were discovered after approval, sometimes decades later, sometimes only in animals.

> ASK YOUR DOCTOR
> *Given that the mechanism of action is unknown for my medication, what is the basis for expecting long-term benefit versus short-term symptom management?*

What the Labels Say the Drugs Can Do

The approved indications vary more than patients might assume. Lithium is approved for acute manic episodes and maintenance — but not for bipolar depression. Seroquel carries the broadest bipolar approval: acute mania (monotherapy and adjunct), bipolar depression (monotherapy), and maintenance (adjunct to lithium or divalproex). Lamictal is approved only for maintenance — delaying the time to recurrence of mood episodes — and its label specifies that "the effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established." Depakote is approved for acute mania only, and its label says so directly: "The safety and effectiveness of Depakote for long-term use in mania, i.e., more than 3 weeks, has not been demonstrated in controlled clinical trials." Abilify is approved for acute manic and mixed episodes but not for bipolar depression or maintenance.

Trial durations behind these approvals are brief. Depakote's mania approval rests on 3-week trials. Seroquel's mania monotherapy trials ran 12 weeks. Abilify's mania trials were short-term. Lamictal's maintenance trials, the longest in the group, evaluated time to recurrence of mood episodes rather than sustained improvement. These drugs are prescribed for decades based on trial data measured in weeks.

No drug in this group has demonstrated mortality reduction in controlled trials. None has shown reversal or cure of bipolar disorder. The labels document symptom management over short periods, and the prescribing information for every one of them advises clinicians who use the drug long-term to "continually reevaluate" or "periodically reassess" whether continued treatment is warranted.

> ASK YOUR DOCTOR
> *My medication was approved based on trials lasting [3/6/8/12] weeks. What evidence supports using it for years or decades?*

The Metabolic Cost

The two antipsychotics in this group — Seroquel and Abilify — carry metabolic warnings that occupy multiple pages of their labels. Seroquel's metabolic section documents hyperglycaemia "in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death." The label acknowledges that "precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available."

Weight gain is documented across the class but varies dramatically. In bipolar mania monotherapy trials, 21% of adult Seroquel patients gained 7% or more of their body weight, versus 7% on placebo. In bipolar depression trials, the figure was 8% versus 2%. For children and adolescents the numbers are worse: 21% of adolescents with schizophrenia gained 7% or more on Seroquel versus 7% on placebo, and in an open-label extension study, 45% of paediatric patients gained that much after 26 weeks. The mean weight increase after 26 weeks of treatment was 4.4 kg. Depakote reported weight gain in 8–9% of patients in its mania and epilepsy trials. For Abilify, 5.2% of pooled paediatric patients with schizophrenia and bipolar mania gained 7% or more of body weight, versus 1.6% on placebo — and in an open-label extension, 32.8% gained that much after 26 weeks.

Fasting glucose shifts compound the picture. In short-term adult trials, 2.4% of Seroquel patients shifted from normal fasting glucose to 126 mg/dL or above, versus 1.4% on placebo. For patients who started with borderline glucose (between 100 and 126), 11.7% crossed the diabetes threshold — essentially the same rate as placebo (11.8%), which raises a question the label does not address: whether the drug is accelerating a trajectory or whether the population is already metabolically vulnerable.

Seroquel's label documents shifts in cholesterol, triglycerides and LDL across indications. In schizophrenia trials, 18% of Seroquel patients shifted to total cholesterol above 240 mg/dL, versus 7% on placebo. Triglycerides above 200 mg/dL: 22% versus 16%. In children with bipolar mania, 22% shifted to triglycerides above 150 mg/dL versus 13% on placebo — and 10% shifted to total cholesterol above 200 mg/dL versus 3% on placebo.

The thyroid findings add another layer. Seroquel produced dose-related decreases in thyroid hormone levels — approximately 20% reduction in total and free T4 at therapeutic doses — during the first six weeks of treatment, maintained without recovery during chronic therapy. In the mania adjunct studies, 12% of Seroquel patients had elevated TSH versus 7% on placebo, and some needed thyroid replacement treatment. Lithium's label documents hypothyroidism and euthyroid goitre as known adverse effects. Depakote reports altered thyroid function tests with "clinical significance unknown".

Three of the five drugs affect thyroid function. For patients taking two of them simultaneously — Seroquel plus lithium is a standard combination — the labels were not

written to address the additive thyroid burden.

> ASK YOUR DOCTOR
> *Have my thyroid levels been tested since I started this medication? If I'm taking more than one of these drugs, is anyone monitoring the combined thyroid effect?*

What the Animals Tell Us

The carcinogenesis sections of these labels describe findings that never made it into the patient-facing summaries. Seroquel produced statistically significant increases in thyroid follicular adenomas in male mice and male rats, and mammary gland adenocarcinomas in female rats "at all doses tested" — including doses as low as 0.3 times the maximum recommended human dose. The label notes that the relevance of both the thyroid tumours and the prolactin-mediated mammary tumours "to human risk is unknown".

Abilify produced mammary gland adenocarcinomas and pituitary adenomas in female mice at doses 0.5 to 5 times the human dose. It also produced adrenocortical carcinomas in female rats at 19 times the human dose. Separately, Abilify caused retinal degeneration in albino rats — and per the label, "additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown."

Depakote produced subcutaneous fibrosarcomas in male rats and benign pulmonary adenomas in male mice. Lamictal was the only drug in the group with no evidence of carcinogenicity in animal studies — though the label notes the highest doses tested "are less than the human dose" on a body surface area basis.

Fertility findings are consistent across the class. Seroquel decreased mating and fertility in both male and female rats at doses as low as 1 times the human equivalent, with effects persisting even after a two-week washout period. The no-effect dose for female rats was 0.01 times the human dose. Depakote caused testicular atrophy and reduced spermatogenesis in rats and dogs, and its post-marketing section reports aspermia, azoospermia, decreased sperm count, decreased spermatozoa motility, male infertility and abnormal spermatozoa morphology in humans. Abilify caused spermatogenesis disturbances and prostate atrophy at higher doses. Lithium's label attributes adverse effects on rat testis and human spermatozoa metabolism to the drug. Lamictal showed no evidence of impaired fertility.

> ASK YOUR DOCTOR
> *Has anyone discussed the fertility implications of my medication with me? If I'm planning to have children, what do the animal studies suggest about the risks?*

What Depakote Does to a Pregnancy

Depakote's boxed warning — the most severe warning the FDA can require — includes “Fetal Risk, particularly neural tube defects, other major malformations, and decreased IQ”. This is not a theoretical concern buried in the animal data. The label documents human evidence: the rate of congenital malformations in babies born to epileptic mothers who used valproate during pregnancy was “about four times higher” than the rate in mothers using other anticonvulsant monotherapies.

The IQ data comes from a prospective cohort study. Children with prenatal valproate exposure had IQ scores of 97 at age 6, compared with 108 for lamotrigine, 105 for carbamazepine, and 108 for phenytoin. Separate observational studies found increased risk of autism spectrum disorders in valproate-exposed children. The label states that valproate “should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control.”

The other labels carry their own pregnancy concerns, though none approaches Depakote's severity. Both Seroquel and Abilify warn that neonates exposed during the third trimester face risk of extrapyramidal and withdrawal symptoms. Lamictal decreases fetal folate concentrations — an effect the label calls “known to be associated with adverse pregnancy outcomes in animals and humans”. Lithium's label reports an increase in cardiac anomalies, particularly Ebstein's anomaly.

For women of childbearing potential taking any of these drugs, the labels collectively present documented harm, partially documented risk, and large zones of the unknown.

> ASK YOUR DOCTOR
> *If I become pregnant while taking this medication, what does the prescribing information say about the specific risks? Is there a pregnancy registry I should know about?*

The Warning That Came Later

Abilify's label contains a warning section not present at the drug's original 2002 approval: Section 5.7, “Pathological Gambling and Other Compulsive Behaviors”. This post-marketing discovery documents that patients on aripiprazole “can experience intense urges, particularly for gambling, and the inability to control these urges.” The label lists additional compulsive behaviours: sexual urges, shopping, eating or binge eating, and “other impulsive or compulsive behaviors”. It notes that “patients may not recognize these behaviors as abnormal” and instructs prescribers to ask specifically about new or intense urges.

This warning did not emerge from controlled trials. It was assembled from post-marketing case reports — the surveillance system that catches what short-term trials cannot. The label acknowledges that "in some cases, although not all, urges were reported to have stopped when the dose was reduced, or the medication was discontinued."

Depakote's post-marketing section contains its own late discovery: "acute or subacute cognitive decline and behavioral changes (apathy or irritability) with cerebral pseudoatrophy on imaging". The brain appeared to shrink on imaging. Both the cognitive changes and the pseudoatrophy "reversed partially or fully after valproate discontinuation".

Seroquel's post-marketing additions include anaphylactic reaction, cardiomyopathy, myocarditis, pancreatitis, retrograde amnesia, rhabdomyolysis, serious liver reactions including hepatic failure, agranulocytosis, intestinal obstruction and sleep apnoea. Lamictal's post-marketing experience added aseptic meningitis — inflammation of the membranes surrounding the brain, sometimes recurring within 30 minutes of re-exposure.

> ASK YOUR DOCTOR
> *Has my medication had any warnings added since it was first approved? Am I experiencing any symptoms that might be drug-related but that I haven't connected to my medication?*

What the Labels Admit Has Not Been Studied

Accumulated gaps in these labels are substantial. Several stand out for their clinical relevance.

Depakote: "The effects of race on the kinetics of valproate have not been studied." Seroquel: "The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies." This admission appears on the label of a drug that is routinely prescribed alongside lithium, valproate, antidepressants and benzodiazepines. The label then adds that Seroquel "potentiated the cognitive and motor effects of alcohol" and cautions against combining it with "other centrally acting drugs" — a category that includes every other drug in this installment.

The combination gap is the defining problem for bipolar pharmacology. Published prescribing data show that 35–48% of bipolar patients take two drugs, and 24–36% take three. One European study found nearly 80% of outpatients with bipolar disorder took a mean of 3.8 medications. Each of these labels was written and approved under conditions of monotherapy or, at most, one specified co-medication. Lithium's label warns of an encephalopathic syndrome — weakness, lethargy, fever, confusion, extrapyramidal symptoms — reported in patients taking lithium plus a neuroleptic. "In some instances, the syndrome was followed by irreversible brain damage." The label adds that this syndrome

"may be similar to or the same as Neuroleptic Malignant Syndrome". Both Seroquel and Abilify are neuroleptics. Neither of their labels cross-references this lithium finding.

Both Seroquel and Abilify acknowledge they have "not been systematically studied, in animals or humans" for their potential for abuse, tolerance or physical dependence. Seroquel as monotherapy for bipolar maintenance "has not been systematically evaluated in controlled clinical trials" — yet it is widely prescribed for exactly this purpose. Lamictal's effect on ovulatory activity: "The clinical significance of the observed hormonal changes on ovulatory activity is unknown." The effect of lamotrigine on hormonal contraceptive preparations other than oestrogen-containing oral contraceptives "has not been systematically evaluated".

Lithium's label presents a different kind of gap. At 530 lines, it is a fraction of the length of the others — not because lithium is simpler, but because it was approved before the FDA required the structured data that modern labels contain. There is no carcinogenesis section. There are no controlled-trial adverse reaction tables with placebo comparisons. The relationship between lithium's documented renal changes "and their association with lithium therapy have not been established". The oldest and most prescribed mood stabiliser carries the thinnest documentation of its own effects.

For paediatric patients, the gaps multiply. Lithium's safety and effectiveness in children under 12 "have not been established". Seroquel has not been established in children under 10 for bipolar mania or under 13 for schizophrenia. Lamictal's safety and effectiveness in patients younger than 18 with bipolar disorder "have not been established". These drugs are prescribed to adolescents and children on the basis of adult trial data, with acknowledged uncertainty about paediatric applicability.

> ASK YOUR DOCTOR
> *Is my drug combination one that has been systematically studied for safety, or are the drugs being prescribed based on individual label data without combination evidence?*

Reproductive and Endocrine Damage

Seroquel elevates prolactin, which suppresses hypothalamic GnRH, reducing gonadotrophin secretion and impairing gonadal steroidogenesis. Documented clinical consequences: galactorrhoea, amenorrhoea, gynaecomastia and impotence. Long-standing hyperprolactinaemia, when associated with hypogonadism, "may lead to decreased bone density in both female and male subjects". And approximately one-third of human breast cancers are prolactin-dependent in vitro — "a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer".

Depakote's post-marketing section reads like a catalogue of reproductive disruption: irregular menses, secondary amenorrhoea, hyperandrogenism, hirsutism, elevated testosterone, breast enlargement, galactorrhoea, polycystic ovary disease. For men: aspermia, azoospermia, decreased sperm count, decreased motility, male infertility and abnormal morphology. Its musculoskeletal section adds fractures, decreased bone mineral density, osteopenia and osteoporosis.

Lamictal's interaction with oral contraceptives creates a two-way problem. Oestrogen-containing contraceptives reduce lamotrigine levels by approximately 50%. During the pill-free week, lamotrigine levels can double, potentially producing adverse effects. Going the other direction, lamotrigine may reduce the efficacy of hormonal contraceptives — the label states "the possibility of decreased contraceptive efficacy in some patients cannot be excluded".

Lithium's label notes impotence and sexual dysfunction among its adverse reactions but provides no systematic data on reproductive outcomes.

> ASK YOUR DOCTOR
> *Is my medication affecting my hormonal balance? If I'm taking both lamotrigine and oral contraceptives, has the dosing been adjusted for the known interaction?*

The Lens, the Brain, the Blood

Seroquel's label recommends slit lamp eye examination "at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment". In dog studies, focal triangular cataracts appeared after 6 months of quetiapine exposure, possibly through inhibition of cholesterol biosynthesis — cholesterol content of the outer lens cortex dropped 25% in female dogs. Lens changes have since been observed in humans on long-term treatment, "but a causal relationship to SEROQUEL use has not been established". Separately, quetiapine deposits an irreversible pigment of unknown identity in rat thyroid glands, co-localised with the drug in follicular epithelial cells. "The functional effects and the relevance of this finding to human risk are unknown." No other drug in this group requires regular eye exams. No other drug leaves an unidentified permanent pigment in an endocrine organ.

Depakote's unique risks are hepatic and pancreatic. Fatal hepatotoxicity occurs predominantly in the first six months. Life-threatening pancreatitis, including haemorrhagic cases with rapid progression to death, has been reported in both children and adults. The thrombocytopenia rate at higher doses — 24% versus 1% in the low-dose group — has implications for bleeding risk, surgical clearance and interactions with anticoagulants. And the cerebral pseudoatrophy finding described earlier — brain shrinkage on imaging,

reversible after discontinuation — appeared only in post-marketing reports, not in the trials that led to approval.

Lamictal's singular risk is Stevens-Johnson syndrome and toxic epidermal necrolysis — potentially fatal skin reactions occurring predominantly in the first three months. Among adult epilepsy patients, approximately 0.3% developed serious rash; among paediatric patients, 0.8%. Concomitant valproate use doubled the risk. Rare cases of rash-related death have occurred.

Lithium carries cardiac, neurological and renal risks that the other labels do not share. Brugada Syndrome unmasking — a cardiac condition with risk of sudden death. Pseudotumour cerebri — increased intracranial pressure that, if undetected, can lead to blindness through optic atrophy. Nephrogenic diabetes insipidus. Morphologic kidney changes including glomerular and interstitial fibrosis, though the label notes similar changes "have also been seen in manic-depressive patients never exposed to lithium". And the encephalopathic syndrome in patients taking lithium plus a neuroleptic: weakness, lethargy, fever, confusion, extrapyramidal symptoms — "in some instances, the syndrome was followed by irreversible brain damage".

Where Seroquel sedates, Abilify activates. The most common adverse reactions in Abilify's adult bipolar mania trials were akathisia (13% vs. 4% placebo), sedation (8% vs. 3%), restlessness (6% vs. 3%), tremor (6% vs. 3%), and extrapyramidal disorder (5% vs. 2%). In paediatric bipolar mania patients, the dose-response was steep: extrapyramidal disorder hit 3.1% on placebo, 12.2% on 10 mg, and 27.3% on 30 mg. Abilify also produced retinal degeneration in albino rats in chronic toxicity studies — "additional studies to further evaluate the mechanism have not been performed". Seroquel's discontinuation syndrome affected 12.1% of patients upon abrupt cessation. Neither antipsychotic carries a labelled taper protocol for bipolar patients.

> ASK YOUR DOCTOR
> *What monitoring is recommended for my specific medication — eye exams, blood work, liver function, kidney function, thyroid panels? Am I receiving all of it on the recommended schedule?*

Questions to Take to Your Doctor

1. What is my medication actually approved to treat — acute mania, bipolar depression, maintenance, or some combination? Am I using it for an approved indication?
2. The trials that supported my drug's approval lasted [3/6/8/12] weeks. What is the evidence for long-term use over years?

3. The mechanism of action for my medication is described as “unknown” or “unclear” in the prescribing information. What does that mean for understanding my treatment?
4. Have my thyroid hormone levels (TSH and free T4) been tested since I started this medication?
5. I'm taking more than one of these medications. Has the combination been systematically studied for safety, or are the drugs being prescribed based on individual label data?
6. What is my current weight compared to when I started treatment? Does the prescribing information predict the degree of weight gain I've experienced?
7. Has anyone discussed the fertility and reproductive implications of my medication with me?
8. If I'm a woman of childbearing potential, what does the prescribing information say about pregnancy risks for my specific medication?
9. Am I receiving all the monitoring my drug's label recommends — including eye exams (Seroquel), liver function tests (Depakote), kidney function tests (lithium), and metabolic panels?
10. Has my medication had any warnings added since it was originally approved? Have I been told about them?
11. Am I experiencing any new urges, compulsive behaviours, or personality changes that might be medication-related?
12. If I wanted to discontinue my medication, what does the prescribing information say about withdrawal symptoms and the recommended taper schedule?

> Disclaimer
> This article is not medical advice. It is a reading of the FDA-approved prescribing information — documents that are public, that your doctor has access to, and that you are entitled to read. The purpose is to help you read what is written and ask better questions.

Sources

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- Lithium carbonate (Lithobid) — NDA 018027, FDA-approved prescribing information, FDA.gov/drugsatfda

- Lamotrigine (Lamictal) — NDA 020241, FDA-approved prescribing information, FDA.gov/drugsatfda
- Divalproex sodium (Depakote) — NDA 018723, FDA-approved prescribing information, FDA.gov/drugsatfda
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