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Phenotype-Gated Evaluation of Bupropion in Parkinsonian Depression: Evidence Calibration and a Dual-Outcome Bayesian Trial

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ABSTRACT

Depression in Parkinson's disease frequently coexists with apathy, anxiety, motor fluctuation, and susceptibility to hallucinations. Bupropion has a pharmacological rationale in this setting, yet the clinical literature is too heterogeneous to separate an apathy-specific benefit from general mood change or dopaminergic adverse effects. To determine whether a phenotype-gated, dual-outcome Bayesian trial can identify a joint antidepressant and anti-apathy advantage while constraining psychosis-related harm. A structured evidence matrix was constructed from 23 publications comprising seven clinical investigations, eleven case reports or case series, and five synthesis or guidance records. Exact numerical observations were retained only when the denominator, instrument, and assessment interval were reported. These observations set the eligibility restrictions, outcome domains, follow-up duration, and safety margin for a double-dummy comparison of bupropion XL with sertraline. Monte Carlo experiments evaluated three sequential analyses at total enrolments of 80, 160, and 240. Joint efficacy required a posterior probability greater than 0.975 that both standardized apathy and depression effects favored bupropion; harm stopping required a posterior probability greater than 0.95 that the psychosis-related event excess exceeded five percentage points. The literature contained five abstract-only records (21.7%) and eleven case-based reports (47.8%). Among reports with compatible paired scores, decreases ranged from 22.4% to 76.0% for depression scales, while a gait score decreased by 11.9% without statistical significance. Under no treatment advantage, the simulated probability of an efficacy decision was 0.0024 and mean enrolment was 111.5. Standardized advantages of 0.45 for apathy and 0.35 for depression yielded an efficacy-decision probability of 0.587 and mean enrolment of 198.1. When the bupropion psychosis-related event rate was 15% and the comparator rate was 3%, the harm-stop probability was 0.641 and mean enrolment fell to 175.4. A dual-outcome sequential trial can distinguish joint symptomatic benefit from mood-only improvement and can terminate early when clinically important neuropsychiatric harm emerges. The design answers a narrower and more clinically actionable question than unrestricted antidepressant efficacy: whether bupropion benefits depressed patients with prominent apathy, stable dopaminergic therapy, and low psychosis liability.

Keywords: Parkinson's disease; bupropion; depression; apathy; Bayesian sequential trial; psychosis; neuropsychiatry

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1. INTRODUCTION

Parkinson's disease is conventionally recognized through bradykinesia, rigidity, tremor, and postural impairment, but disability and quality of life are also strongly determined by affective, motivational, cognitive, autonomic, and sleep disturbances. These non-motor manifestations may precede a motor diagnosis, fluctuate with dopaminergic state, and remain unrecognized when reduced speech, slowed movement, fatigue, or sleep disruption is attributed solely to neurodegeneration.[2–4] Depression is therefore not a peripheral comorbidity. It alters adherence, caregiver burden, participation in rehabilitation, perception of motor disability, and the clinical meaning of apparent treatment response. Behavioral management consequently requires coordinated neurological and psychiatric assessment.[40] The diagnostic problem is compounded by overlap among depressed mood, anhedonia, apathy, cognitive slowing, and medication-related "off" periods. A treatment study that collapses these features into a single total score can produce an average improvement without identifying which neuropsychiatric process changed.

Antidepressant selection in Parkinson's disease remains an area of clinical uncertainty. Serotonergic agents are commonly chosen because their use is familiar and their interaction profile is usually manageable, yet randomized evidence is limited and between-study comparisons are weakened by small samples, different diagnostic thresholds, short observation periods, and inconsistent motor assessments.[5,6] Bupropion is distinctive because it inhibits norepinephrine and dopamine transporters without direct serotonergic reuptake inhibition. Its lower propensity for sexual dysfunction, weight gain, and sedation can be advantageous in patients already troubled by fatigue, orthostatic symptoms, or reduced initiative.[35,36] The same pharmacology creates concern: increasing catecholaminergic transmission may exacerbate agitation, insomnia, tremor, dyskinesia, hallucinations, or confusion in vulnerable individuals.

The biological argument for bupropion is strongest when depression is accompanied by apathy. Mesolimbic and prefrontal catecholaminergic deficits have been associated with loss of interest, energy, executive drive, and reward responsiveness in Parkinson's disease.[8] The compartmental handling of dopamine may also influence therapeutic opportunity and vulnerability to dopaminergic toxicity.[9] Apathy is not synonymous with sadness and may persist despite improvement in conventional depressive symptoms. Its reported frequency and association with functional decline justify direct measurement rather than inference from a depression scale.[39] The hypothesis that bupropion may be particularly suitable for this phenotype has appeared in clinical commentary and specialist recommendations,[7,31] but a confirmatory trial has not separated motivational benefit from general mood improvement.

Published clinical observations provide both encouragement and caution. Rapid or sustained decreases in Hamilton Depression Rating Scale scores have been described in individual patients,[10,12] and small open studies reported improvement in depressive severity or nonmotor daily living.[21,26] A randomized conference report favored bupropion over sertraline after six weeks, although the absence of a full report prevents appraisal of allocation, masking, concomitant therapy, and missing observations.[25] An early mixed controlled and open investigation found motor improvement but also excitement, nausea or vomiting, restlessness, hallucinations or confusion, and dyskinesia.[13] Separate case observations described dystonia, myoclonus, hyponatremia, and interference with dopamine-transporter imaging.[18,19,27] These findings do not establish incidence, yet they identify adverse outcomes that require active ascertainment rather than reliance on spontaneous reporting.

The existing literature also illustrates why a conventional two-arm trial with a single depression end point would be insufficient. Improvement confined to mood would not validate the proposed motivational mechanism. Improvement in motor performance could indirectly alter depression ratings, especially for instruments containing somatic items. Conversely, worsening hallucinations could be diluted within a general adverse-event total. Concomitant changes in dopamine agonists, levodopa, psychotherapy, or other antidepressants would make attribution difficult, as illustrated by reports in which bupropion was combined with rasagiline, cognitive-behavioral therapy, or modified levodopa regimens.[11,17,20] The clinical question must therefore specify phenotype, comparator, treatment stability, coprimary outcomes, and a neuropsychiatric stopping rule.

The present study asks: can a phenotype-gated, sequential randomized design identify a bupropion advantage that is simultaneous for apathy and depression, independent of clinically important motor deterioration, while stopping when psychosis-related risk becomes unacceptable? This question differs from asking whether any published report favors bupropion. It defines the population most likely to display the hypothesized catecholaminergic benefit, requires concordant change in two neuropsychiatric domains, and treats hallucination or confusion as a decision-limiting outcome. The study combines a transparent map of the clinical literature with reproducible Monte Carlo experiments. No simulated participant is represented as a treated patient; the computations quantify how the planned decision rules behave before clinical recruitment.

2. METHODS

2.1. Variable coding

The analytical corpus comprised the 23 records and the two detailed study tables reported in the attached clinical review.[1] Each record was coded by publication year, region, report type, full-text availability, number exposed to bupropion when stated, indication, dose range, treat-

ment duration, comparator, use of a named outcome instrument, direction of depressive and motor findings, safety ascertainment, and presence of an adverse signal. Record-level mapping was selected because broad evidence fields with heterogeneous designs should be characterized before causal pooling is attempted.[33] Records were retained as distinct publications; participants were not pooled across incompatible designs. The resulting matrix contained seven clinical investigations, eleven case reports or case series, and five records of evidence synthesis, guidance, or expert consensus.

Numerical change was calculated only when both pre-treatment and follow-up values were stated for the same instrument. The proportional decrease was

$$R = 100 \times \frac{Y_0 - Y_t}{Y_0}, \tag{1}$$

where Y_0 is the pre-treatment score and Y_t is the reported follow-up score. This transformation permits a descriptive comparison of relative change while preserving the identity of each instrument. It does not make the scales interchangeable, does not correct for natural history or expectancy effects, and is not interpreted as a pooled treatment effect. Change values stated without a pre-treatment score, such as the reported Montgomery–Åsberg Depression Rating Scale decrease of 17.6 points in one open study, were presented in their native units but excluded from proportional calculations.

Publication records were assigned to three broad display groups: case evidence, clinical investigations, and synthesis or guidance. Full-text status was shown independently because five conference records lacked sufficient reporting for assessment of allocation procedures, missing observations, or adverse-event collection. The national prescription cohort was used only to describe treatment frequency; its 6.8% bupropion prescription rate was not interpreted as efficacy. Likewise, meta-analytic findings that grouped bupropion with other atypical antidepressants were treated as indirect evidence.[29,30,32]

2.2. Target population and randomized comparison

The intended population comprises adults aged 40–80 years with clinically established Parkinson's disease, a current depressive disorder, and prominent apathy despite stable antiparkinsonian therapy. Prominent apathy is defined by a Lille Apathy Rating Scale score meeting a prespecified severity threshold and confirmation that reduced motivation is not explained by delirium, a current manic state, or severe cognitive impairment. Eligibility requires unchanged levodopa-equivalent dosage for four weeks before randomization and an expectation that the regimen can remain stable for the 16-week treatment period. Active hallucinations, delusions, a psychotic disorder, seizure disorder, current eating disorder, uncontrolled hypertension, recent monoamine-oxidase A inhibitor exposure, and imminent suicide risk are exclusion criteria. Prior hallucinations that resolved more than six months earlier trigger enhanced monitoring but do not automatically exclude participation when an independent psychiatrist confirms stability.

Participants are randomized 1:1 to bupropion XL or sertraline using a double-dummy procedure. Randomization is stratified by site, Hoehn–Yahr stage (I–II versus III), and current monoamine-oxidase B inhibitor use. Bupropion XL begins at 150 mg each morning and increases to 300 mg after two weeks when tolerated. Sertraline begins at 50 mg and increases to 100 mg on the same schedule. Dose reduction is permitted for insomnia, agitation, gastrointestinal intolerance, blood-pressure elevation, or motor worsening; return to the higher dose is permitted once. Psychotherapy initiated before enrolment may continue unchanged, but new structured psychotherapy is deferred unless clinically necessary.

The primary assessment occurs at week 16. Intermediate clinical visits at weeks 2, 4, 8, and 12 include adverse-event questioning, blood pressure, orthostatic measurements, medication reconciliation, the Movement Disorder Society Unified Parkinson's Disease Rating Scale motor examination, and a brief hallucination and delusion interview. Serum sodium is measured before treatment and at weeks 2 and 8 because hyponatremia has been reported in an exposed patient.[19] Dopamine-transporter imaging is prohibited during treatment and for four weeks after the last bupropion dose because transporter occupancy can confound scan interpretation.[18]

2.3. Outcomes and estimands

The two primary outcomes are standardized week-16 changes in apathy and depression. Apathy is measured with the Lille Apathy Rating Scale and depression with the Montgomery–Åsberg Depression Rating Scale. Scores are oriented so that positive standardized change denotes improvement. The treatment effects δ_A and δ_D are the adjusted mean differences between bupropion and sertraline for apathy and depression, respectively, divided by the pooled within-arm standard deviation. The primary estimand is the effect of assignment under continued follow-up regardless of dose reduction, with multiple imputation for missing week-16 values using site, stratification variables, earlier scores, motor change, and treatment adherence.

The key safety outcome is a composite of new hallucinations, delusions, or clinically consequential confusion adjudicated by a blinded neuropsychiatry committee. This composite was chosen because psychotic and confusional phenomena have been reported during bupropion exposure and because dopaminergic vulnerability is central to the clinical decision.[37] Separate secondary outcomes include response defined by at least 50% improvement in depression, remission, clinician-rated global improvement, quality of life, daytime sleepiness, freezing of gait, motor score, dyskinesia, anxiety, insomnia, nausea,

orthostatic change, and treatment discontinuation. An apathy response is analyzed only as a secondary binary outcome; the continuous score retains more information for the primary analysis.

To separate motivational improvement from motor change, the primary model adjusts for pre-treatment motor severity and week-16 motor change. A sensitivity analysis removes motor-related or somatic depression items before standardization. A second sensitivity analysis estimates the effect among participants whose dopaminergic therapy remains unchanged throughout the trial. Concordance between these analyses would support a neuropsychiatric effect that is not merely a consequence of improved mobility.

2.4. Bayesian sequential analysis

Three analyses are planned after total enrolments of 80, 160, and 240 participants with equal allocation. Standardized outcomes are modeled jointly with within-participant correlation $\rho = 0.40$. Each treatment effect receives a weakly regularizing normal prior,

$$\delta_k \sim \mathcal{N}(0, 0.5^2), \qquad k \in \{A, D\}. \tag{2}$$

For computational calibration, the observed arm difference $\widehat{\delta}_k$ at a given analysis has sampling variance $2/n$, where n is the number per arm. The posterior variance and mean are

$$V_k = \left(0.5^{-2} + \frac{n}{2}\right)^{-1}, \qquad m_k = V_k \left(\frac{n}{2}\widehat{\delta}_k\right). \tag{3}$$

These expressions show how early estimates are modestly shrunk toward no difference and how the influence of the prior declines as enrolment increases. The analysis software uses the bivariate sampling distribution for data generation and a product-normal approximation for the joint posterior probability. A full trial analysis would use a multivariate regression with site effects and missing-observation imputation, but the closed form above makes every calibration decision auditable.

Efficacy is declared when

$$\Pr(\delta_A > 0, \delta_D > 0 \mid \mathcal{D}) > 0.975 \tag{4}$$

and the posterior probability that the psychosis-related event excess exceeds 0.05 is below 0.10. Futility is declared when the posterior probability that both $\delta_A > 0.20$ and $\delta_D > 0.15$ is below 0.10. Thus, efficacy requires convincing superiority in both domains, whereas early futility asks whether a jointly relevant effect remains plausible. Mood improvement without apathy improvement, or apathy improvement without depression improvement, cannot satisfy the primary rule.

Psychosis-related event probabilities receive independent Jeffreys priors, $p_B, p_S \sim \mathrm{Beta}(0.5, 0.5)$, for bupropion and sertraline. Harm stopping occurs when

$$\Pr(p_B - p_S > 0.05 \mid \mathcal{D}) > 0.95. \tag{5}$$

The five-percentage-point margin denotes a clinically important absolute excess rather than any numerical difference. An independent monitoring committee may stop for a single catastrophic event or a pattern not captured by the composite, so the probability rule supplements rather than replaces clinical judgment.

2.5. Monte Carlo experiments

The decision rules were examined with pseudo-random seed 172903. Each parameter combination generated correlated standardized outcomes with unit marginal variance and correlation 0.40, together with binomial psychosis-related events. Earlier participant observations were retained at each later analysis, and only the newly enrolled participant increments were generated. A 5×5 grid crossed apathy and depression advantages of 0.00, 0.15, 0.30, 0.45, and 0.60; 6,000 replicate trials were generated in every grid cell with event probabilities of 0.03 in both arms. Three selected conditions used 20,000 replicates: no symptomatic advantage with equal event rates, a joint advantage of 0.45 for apathy and 0.35 for depression with equal event rates, and the same joint advantage with event rates of 0.15 for bupropion and 0.03 for sertraline. The 15% value corresponds to the observed three-of-twenty hallucination or confusion count in the early mixed-design investigation; it is used as a stress condition and not as an incidence estimate.

Recorded quantities were the probabilities of efficacy, futility, and harm decisions, together with mean and median enrolment. Monte Carlo standard errors were calculated as $\sqrt{\widehat{p}(1-\widehat{p})/M}$, where M is the number of replicates. With 20,000 replicates, the maximum standard error for a decision probability is 0.00354. All code, the publication matrix, numerical change table, and generated comma-separated outputs accompany the manuscript.

3. RESULTS AND DISCUSSION

3.1. Composition and development of the evidence field

The 23-record corpus was dominated by case evidence and small clinical investigations (Table 1). Eleven records (47.8%) were case reports or a three-person case series, seven (30.4%) were clinical investigations, and five (21.7%) were syntheses, guidance, or expert consensus. Five clinical records were available only as conference abstracts. Although the national prescription cohort included 7,868 veterans with depression and Parkinson's disease, it did not report bupropion effectiveness or tolerability and therefore contributes utilization information rather than a treatment estimate.[16] The apparent size of the literature must not be confused with the number of participants who received bupropion under prospective outcome assessment.

This composition explains why a qualitative impression of frequent improvement cannot support a causal claim. Case reports selectively preserve unusual ben-

Table 1. Composition of the 23-record evidence corpus.

Record group	n	Percent
Case reports or case series	11	47.8
Clinical investigations	7	30.4
Synthesis, guidance, or consensus	5	21.7
Abstract-only records	5	21.7
Published from 2008 through 2021	15	65.2

efit or harm, open studies cannot separate treatment from expectancy and time, and abstract-only reports omit essential analytical detail. Formal evidence grading likewise places uncontrolled observations below randomized comparisons.[34] The role of the corpus is consequently to identify plausible phenotypes, feasible doses, outcome domains, and safety events for prospective testing.

The equal-area record field in Figure 1 makes the reporting imbalance visible without allowing the large prescription cohort to dominate by sample size. Gold cells outnumber controlled or open clinical-study cells, and red borders identify every abstract-only publication. Chronological ordering also shows that later publication did not consistently produce larger or more complete efficacy reports. This visual organization is deliberately record-based: a sample-size-weighted display would imply that prescribing frequency and controlled efficacy are commensurable.

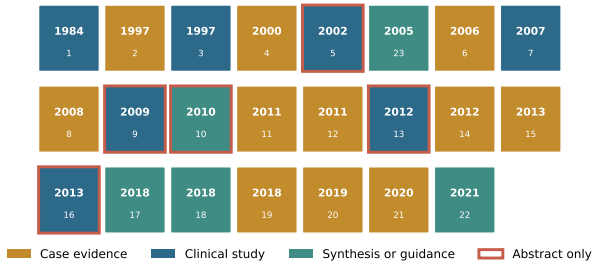

Figure 1. Publication record field.

The cumulative trajectories in Figure 2 reveal two distinct phases. Only one clinical investigation preceded 1997. After 2008, case evidence accumulated more quickly than controlled evidence, reaching eleven records by 2020, while the clinical-study curve stopped at seven by 2013. Synthesis and guidance records then increased despite the absence of a corresponding expansion in controlled trials. Consensus can assist practice when direct evidence is sparse,[28] but it cannot substitute for randomized outcome ascertainment.

The divergence between accumulating commentary and stagnant controlled evidence supports a prospective design rather than another unrestricted literature summary. It also argues for a narrow claim. The trial should not attempt to establish bupropion as a universal antidepressant for Parkinson's disease; it should test the mechanistically coherent subgroup with apathy and low psychosis

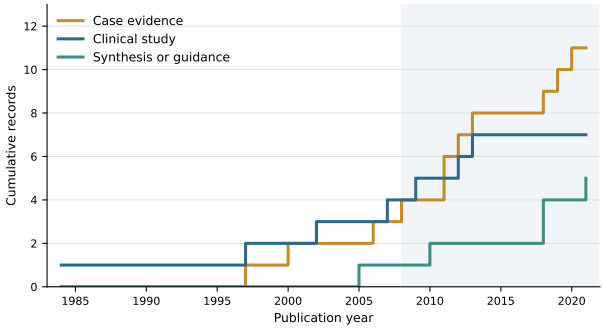

Figure 2. Cumulative publication record counts.

liability.

3.2. Magnitude and interpretability of reported symptom changes

Seven paired numerical observations permitted proportional description (Table 2). Depression-score decreases ranged from 22.4% in a three-person compulsive-eating case series to 76.0% in a single patient followed for seven months. The 12-week Korean open study reported a mean Hamilton Depression Rating Scale decrease from 23.11 to 11.12, equivalent to 51.9%. A patient with panic disorder showed decreases of 46.9% on the depression scale and 54.8% on the anxiety scale while also beginning cognitive-behavioral therapy. These values describe reported change; they do not identify the portion caused by bupropion.

The scale-specific display in Figure 3 preserves the distinction among depression, anxiety, and gait. The largest proportional decreases arise from single-patient reports, whereas the group mean from the 15-person open study lies near the center of the depression observations. The gait decrease is substantially smaller and was reported as statistically non-significant.[22] This pattern is compatible with a neuropsychiatric signal but cannot establish that motor improvement mediates or accompanies mood change.

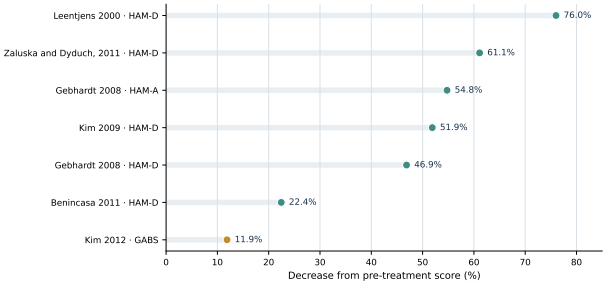

Figure 3. Reported within-study score decreases.

Interpretation requires particular restraint because percentage change depends on the pre-treatment value, follow-up intervals range from ten days to seven months, and several reports include concomitant interventions. The fast Hamilton score decrease from 18 to 7 within ten days is clinically notable but shorter than the usual pe-

Table 2. Reported paired scores retained for proportional description.

Study	Instrument	Pre-treatment	Follow-up	Decrease (%)
Benincasa et al., 2011	HAM-D	14.70	11.40	22.4
Gebhardt et al., 2008	HAM-D	32.00	17.00	46.9
Gebhardt et al., 2008	HAM-A	42.00	19.00	54.8
Kim et al., 2009	HAM-D	23.11	11.12	51.9
Leentjens et al., 2000	HAM-D	25.00	6.00	76.0
Załuska and Dyduch, 2011	HAM-D	18.00	7.00	61.1
Kim et al., 2012	GABS	34.50	30.40	11.9

riod needed to judge sustained antidepressant response. Conversely, the seven-month single-patient observation provides duration but no comparator. The open six-month investigation reported a 17.6-point Montgomery–Åsberg decrease, a 22.1-point Global Assessment of Functioning increase, improvement in non-motor daily living, and selected quality-of-life domains;[26] without a control arm, correlated change across domains remains vulnerable to expectancy, regression toward the mean, and clinical contact.

Evidence for compulsive behavior and anxiety is hypothesis-generating rather than confirmatory. Three patients with dopamine-agonist-associated compulsive eating reduced food intake within three to four weeks and lost weight during bupropion treatment.[15] One patient with panic disorder improved while receiving both bupropion and cognitive-behavioral therapy.[17] A patient with dopamine dysregulation syndrome did not improve after eight weeks.[23] These contrasting observations favor focused secondary outcomes and stable concomitant treatment; they do not justify broad claims across impulse-control, anxiety, and mood disorders.

3.3. Safety signals and design consequences

The most detailed count of adverse events came from the 20-person mixed controlled and open investigation (Figure 4). Excitement occurred in nine participants, nausea or vomiting in eight, restlessness in four, hallucinations or confusion in three, and postural tremor and dyskinesia in one each. Five participants had dose-limiting events. Because parts of the study lacked placebo comparison and adverse-event timing was incompletely described, these frequencies cannot be treated as modern incidence estimates. They nevertheless identify events that are clinically coherent with catecholaminergic stimulation and must be solicited at early visits.

Isolated reports expand the monitoring set. Severe dystonia and dyskinesia appeared two days after treatment began and resolved after withdrawal;[27] propriospinal myoclonus followed bupropion initiation with a simultaneous memantine increase; and severe hyponatremia resolved after discontinuation. A systematic review of bupropion-associated movement disorders found reports of tremor, falls, dystonia, dyskinesia, parkinsonism,

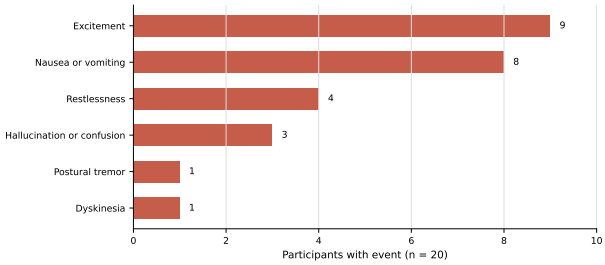

Figure 4. Adverse-event counts in a 20-person study.

and myoclonus but emphasized incomplete neurological examinations and uncertain attribution.[14] These observations support scheduled motor examinations, dose-dechallenge documentation, sodium measurement, and blinded adjudication rather than a single undifferentiated tolerability total.

Combination treatment deserves separate attention. A retrospective review of 28 men receiving selegiline with antidepressants included three bupropion exposures and reported no discontinuation attributed to that combination; the only serotonin syndrome occurred with fluoxetine.[24] This small experience is reassuring but cannot exclude hypertension, agitation, or dopaminergic adverse effects. Stratifying randomization by monoamine-oxidase B inhibitor use and retaining a stable dose allows the trial to estimate whether combination status modifies treatment response without confusing exposure changes with outcome changes.

3.4. Operating characteristics of the sequential design

The complete 5×5 simulation surface demonstrates that an efficacy decision requires concordant effects (Figure 5). With no apathy advantage, the efficacy probability remained at or below 0.029 even when the depression advantage reached 0.60. With no depression advantage, the maximum probability was 0.028. When both standardized advantages were 0.30, the efficacy probability was 0.321; it rose to 0.714 at 0.45 in both domains and 0.833 at 0.60 in both domains. This shape is a direct consequence of the joint posterior rule and protects against interpreting mood-only improvement as evidence for the hypothesized apathy-responsive phenotype.

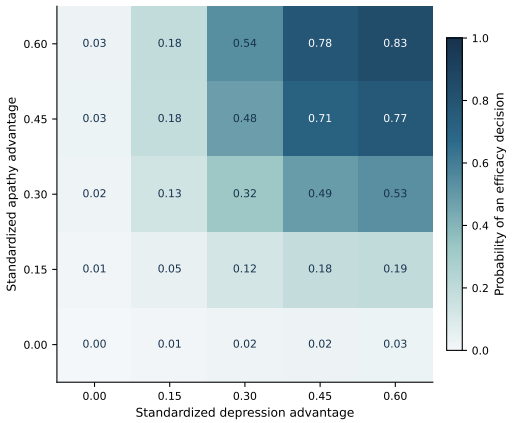

Figure 5. Joint efficacy-decision probabilities.

The three selected conditions quantify error, sensitivity, and safety behavior (Table 3). With no symptomatic advantage and equal 3% event probabilities, 47 of 20,000 simulated trials declared efficacy, corresponding to 0.0024 with a Monte Carlo standard error of 0.00034. Futility occurred in 99.750%, mean enrolment was 111.5, and the median was 80. The rule therefore rejects unpromising treatment early while maintaining a very low false efficacy probability under the modeled null condition.

Table 3. Selected operating characteristics from 20,000 replicates per condition.

Condition	Efficacy	Futility	Harm stop	Mean N
No advantage; event rates 3% and 3%	0.0024	0.9975	0.0002	111.5
$\delta_A = 0.45$, $\delta_D = 0.35$; event rates 3% and 3%	0.5872	0.4127	0.0001	198.1
Same effects; event rates 15% and 3%	0.0022	0.3570	0.6409	175.4

For a joint standardized advantage of 0.45 in apathy and 0.35 in depression, the efficacy probability was 0.587 and mean enrolment was 198.1. This result is deliberately more conservative than the power of a single depression end point because both clinical claims must be supported. Investigators seeking 80% probability at these exact effects would need either a larger maximum sample, a less stringent posterior threshold, or a more prognostically efficient covariate model. Relaxing the joint requirement would answer a different question and is not preferred. A blinded sample-size re-estimation based on pooled outcome variance could be added without revealing treatment differences, provided the maximum enrolment is declared in advance.

When the psychosis-related event probability was 15% with bupropion and 3% with sertraline, the harm rule stopped 64.1% of simulated trials and reduced mean enrolment to 175.4. Efficacy declarations fell to 0.22%, even though the symptomatic effects were retained. This behavior is clinically appropriate: neuropsychiatric benefit should not support adoption when a large psychosis-related excess is credible. The rule is less sensitive to smaller excesses, so continuous committee review and event-level seriousness remain essential.

The stopping-time distribution in Figure 6 shows why mean enrolment alone is incomplete. Under no advantage, 72.7% of trials stopped at the first analysis, 15.3% at the second, and 12.0% reached 240. Under the joint target, 13.3% stopped at 80, 25.8% at 160, and 60.9% reached the maximum. With a 15% event probability, 27.2% stopped at 80, 26.3% at 160, and 46.4% reached 240. Sequential monitoring therefore concentrates participant exposure where the benefit–risk question remains unresolved.

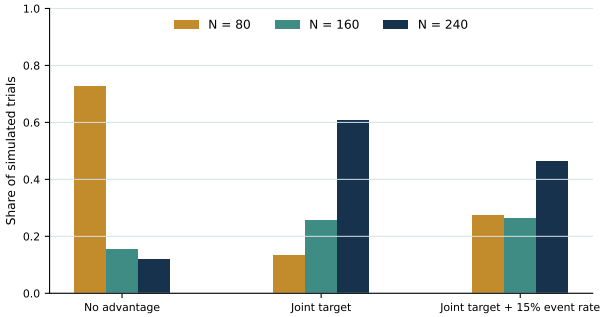

Figure 6. Distribution of trial stopping enrolment.

These computations answer a design question, not a therapeutic one. Their numerical probabilities depend on the assumed standardized effects, correlation, event rates, prior scale, and missing-observation behavior. The evidence corpus does not estimate these quantities precisely. The values were chosen to span no effect through large joint effects and to test a psychosis-related rate observed in an early small study. Re-running the supplied code with alternative values is therefore part of protocol development, and a clinical conclusion must await randomized participants.

3.5. Clinical interpretation and trial feasibility

The design focuses on patients with both depression and prominent apathy because this phenotype gives the pharmacological hypothesis a falsifiable form. Bupropion's action on norepinephrine and dopamine transport does not imply benefit in every depressed patient with Parkinson's disease. Patients whose low mood closely follows levodopa wearing-off may require optimization of dopaminergic timing; those with active hallucinations may incur disproportionate risk; and those without apa-

thy do not test the motivational hypothesis. Enrichment improves mechanistic coherence at the cost of narrower generalizability.

Sertraline is a clinically relevant comparator rather than an inert control. A placebo arm would clarify absolute efficacy but could be difficult in a symptomatic depressive population and would enlarge the required sample. The active comparison addresses whether the catecholaminergic profile offers an advantage beyond a commonly used serotonergic treatment. The double-dummy schedule and matched titration reduce expectation differences. A small nested placebo group could be considered only if ethical review and rescue procedures are satisfactory, but it is not necessary for the primary question.

Sixteen weeks balances antidepressant assessment against prolonged exposure to an ineffective or activating drug. The six-week randomized conference report may have been too short to establish durability, whereas the 12-week and six-month open studies indicate that longer follow-up is feasible. Early visits remain dense because agitation, insomnia, blood-pressure changes, and motor complications may emerge soon after titration. Continued follow-up after dose reduction preserves the assignment estimand and avoids an artificially favorable analysis restricted to tolerant participants.

The design also resolves several recurrent interpretive problems. First, co-primary continuous outcomes prevent a large change in one domain from masking absence of change in the other. Second, adjustment for motor change reduces contamination of mood scores by improved mobility. Third, stable dopaminergic therapy limits confounding by levodopa or agonist modification. Fourth, adjudicated psychosis-related outcomes prevent severe but infrequent events from disappearing within general side-effect counts. Fifth, sequential futility reduces exposure when a jointly relevant effect is unlikely.

Residual limitations remain. The evidence matrix depends on published reporting and includes conference abstracts with little methodological detail. Selective publication can inflate the apparent frequency of benefit.[38] Proportional score decreases compare neither randomization groups nor common instruments. The Monte Carlo model assumes normally distributed standardized change, equal marginal variances, a fixed correlation, complete ascertainment of the safety composite, and no site heterogeneity. Real recruitment may also be limited by the simultaneous requirements for depression, apathy, stable medication, and low psychosis liability. These limitations should be addressed through a blinded internal pilot that measures recruitment, retention, outcome variance, and completion of week-16 assessments without testing treatment efficacy.

4. CONCLUSION

The study asked whether a phenotype-gated sequential trial could determine if bupropion provides a joint apathy and depression advantage over sertraline while limiting psychosis-related risk in Parkinson's disease. The computational answer is qualified but affirmative. The joint rule rarely declared efficacy when neither outcome favored bupropion, rejected one-domain improvement as insufficient, and identified 58.7% of trials with standardized advantages of 0.45 for apathy and 0.35 for depression under equal safety rates. When the bupropion psychosis-related event rate rose to 15% against 3% with sertraline, 64.1% of trials stopped for harm. These properties support a 16-week, double-dummy, multicenter trial in depressed patients with prominent apathy, stable dopaminergic treatment, and no active psychosis, while indicating that a larger maximum sample would be required for 80% detection probability at the joint target effects. The therapeutic question remains open until such participants are randomized; the present contribution is a reproducible decision design that specifies what evidence would be sufficient for benefit, futility, or harm.

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