

**Methods/Research · Educational evidence summary**

A protocol for evaluating anticholinergic burden and cognition

This methods article addresses a protocol for evaluating anticholinergic burden and cognition.

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Abstract

Studies of anticholinergic burden and cognition can address different questions: concurrent association, prediction of later performance, or the effect of changing medication exposure. This article proposes a protocol framework that keeps those objectives separate. It does not report recruitment, new cognitive assessments, or a completed analysis. The proposed methods specify a target population, one primary cognitive outcome, the timing and completeness of medication ascertainment, and the exact source-specific exposure method. They distinguish baseline differences from within-person change, preserve missing medication evidence, and plan how competing explanations and incomplete follow-up will be examined. Existing adult psychosis and pediatric reviews illustrate why population and outcome scope must accompany any interpretation; neither supplies a universal threshold for this protocol. A future report would present estimates with uncertainty and the prespecified limitations of its design. The aim is a reproducible study question, not a synthetic UnifiedACB score or a promise of cognitive benefit from medication changes.

Introduction

“Burden and cognition” is too broad to define a study. Cognition may refer to learning, attention, processing speed, a composite battery, or perceived difficulty in daily life. Exposure may refer to prescriptions, actual administration, a single visit, or a sustained regimen. Different choices can produce different findings without answering the same question.

The first decision is therefore the intended inference. A cross-sectional study can describe an association at an assessment. A prospective study can evaluate whether earlier exposure predicts later outcomes. A study of a supervised treatment change addresses another question and requires attention to why that change occurred. These designs should not be presented as interchangeable evidence of causation.

Methods

Define the population and primary outcome

The full protocol would specify age range, clinical conditions, care setting, inclusion criteria, and the group to which the result is intended to apply. Combining populations would require a rationale and a



plan to examine relevant heterogeneity. Adult and pediatric participants should not be pooled merely because the same medicine names can be looked up in a scale.

A primary cognitive outcome would be selected before analysis, including its instrument, domain, scoring direction, and assessment interval. Other domains and patient-reported outcomes could be secondary measures. The protocol should distinguish objective test performance from everyday function or school achievement rather than infer one from the other without measuring it.

Assessment conditions would be recorded sufficiently to interpret the result. Language, sensory or motor limitations, clinical state, and the ability to complete testing may affect what a score represents. Repeated testing requires a plan for interpreting change, including the possibility that familiarity with the task contributes to performance.

Define medication exposure independently of the outcome

The exposure method would name the exact scale and version and follow its published rules. It would specify whether the medication history reflects orders, dispensing, reported use, or observed administration, and how the exposure window relates to cognitive assessment. Scheduled and as-needed medicines would be distinguished rather than treated as equivalent daily exposure by default.

Each medicine would retain its identity and relevant route or formulation. Unresolved products and missing source entries would remain explicit. If an established source-specific burden method is used, the analysis would follow that method and report coverage. It would not average ordinal categories across scales or create a new UnifiedACB index under the guise of harmonization.

Dose and duration would be collected where relevant and feasible, but their presence would not justify an improvised weighting formula. A dose-aware method needs its own definition and evidence basis. The protocol should state which exposure features its chosen measure captures and which remain separate descriptors.

Specify the analysis before viewing associations

The analysis plan would identify the primary comparison, relevant clinical covariates, and the reasoning linking them to exposure and outcome. Adjusting for every available variable is not automatically appropriate. Some variables may reflect reasons for treatment, some competing explanations, and others consequences of exposure. Their roles should be considered in the study's causal framework.

The plan would address missing medication information, incomplete cognitive testing, and loss to follow-up. Excluding all incomplete cases may select a group that differs from those who could not complete testing. Any missing-data method would require explicit assumptions and sensitivity analyses appropriate to the study, rather than an automatic claim that missingness has been solved.

Sample-size planning, statistical models, subgroup analyses, and multiplicity handling would be completed for the actual design before recruitment or data analysis. This article supplies no invented target sample or expected effect. Analyses added later should be identified as exploratory, with the reason for the change recorded.

Results

No participants were recruited, no cognitive outcomes were collected, and no association estimate was computed for this article. The protocol's current output is a defined set of design decisions that a



future study must resolve. It is not a registered trial, completed observational analysis, or external validation of UnifiedACB.

The cited psychosis synthesis and pediatric cognition review concern different populations and evidence bases. Their conclusions must remain attached to those settings. [Mancini et al., 2025](#) [Ghezzi et al., 2021](#) They motivate careful specification of population and measurement, rather than provide a pooled expected effect that can be inserted into this proposed protocol.

A completed study would report participant flow, exposure completeness, source coverage, outcome availability, estimates with uncertainty, and deviations from the original plan. Null or inconclusive findings should be reported with the same care as positive associations, without interpreting imprecision as proof of no effect.

Discussion

Confounding by indication is central to interpretation. People receiving more complex treatment may differ in illness severity, prior response, comorbidity, or care needs. Those differences can also relate to cognition. Statistical adjustment can address measured factors under stated assumptions; it cannot guarantee that an observational comparison reproduces a randomized treatment contrast.

Time ordering matters as well. Cognitive difficulty may influence treatment choice, adherence, or the accuracy of a medication history. A same-visit association cannot establish which came first. Prospective measurement can improve temporal interpretation, but it does not automatically remove confounding or errors in exposure ascertainment.

Source selection can influence who is classified as exposed. A study should show how much of each regimen is represented and whether conclusions change under justified alternative source-specific analyses. These analyses should remain separate. A convenient average across scales would obscure both the original categories and the coverage differences the sensitivity analysis is meant to examine.

An observed cognitive association also has limited clinical reach. Test performance does not by itself establish an effect on independent living, education, work, or quality of life. A treatment-change study needs to assess relevant benefits and harms of that change, including the condition the medicine was treating. The desired result is a balanced account of outcomes, not a lower burden number at any cost.

Limitations

This framework does not select an instrument, population, exposure threshold, model, or intervention for a specific project. Those decisions require a complete protocol, appropriate expertise, and the necessary study governance. No inference about an individual patient's cognition or medication plan follows from the proposed design alone.

Even a carefully executed study may be limited by exposure misclassification, incomplete source coverage, unmeasured clinical differences, testing constraints, and follow-up. Transparent reporting makes those limits assessable; it does not convert an association into certainty about a mechanism or treatment effect.



Conclusion

A credible study begins with a narrow question and a traceable exposure definition. Preserve the source method, measure the cognitive outcome actually claimed, and report what the design can and cannot establish. That discipline is more informative than treating every burden-cognition association as the same result.

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Disclosure

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