

**Psychiatry · Educational evidence summary**

Separating treatment effect from anticholinergic exposure in cognitive research

This psychiatry article focuses on separating treatment effect from anticholinergic exposure in cognitive research.

UnifiedACB · Published October 3, 2026 · Updated October 4, 2026

Read the current article

<https://unifiedacb.com/articles/068-separating-treatment-effect-from-anticholinergic-exposure-in-cognitive-research/>

Abstract

Studies relating anticholinergic burden to cognition can answer different questions even when they use similar terminology. This methodological analysis distinguishes a descriptive medication association from the effect of changing a treatment strategy. Its evidence basis is the cited psychosis literature and the source-specific structure of UnifiedACB; no new participant data or statistical analysis are reported. The approach separates treatment indication, medication classification, actual exposure, cognitive measurement, and the timing of each. The principal conclusion is methodological: a category-outcome association does not identify the effect of removing one contributor while preserving every other aspect of care. A defensible study must define its population, intervention or exposure contrast, outcome, and observation period before analysis. The framework below identifies design choices and failure modes for future work. It does not claim that a new causal estimate, validated prediction model, or treatment threshold has been produced.

Introduction

A medicine can be associated with cognitive performance because of its pharmacologic effects, because of the condition that led to treatment, or because it accompanies other aspects of care. The medication list observed at an assessment may be the result of years of decisions. Treating that list as though it were randomly assigned can obscure the question a study is actually able to answer.

The objective here is to make the distinction explicit. “Are higher source-specific burden values associated with lower test scores?” differs from “Would a defined medication-review strategy improve cognition compared with usual care?” The first concerns a measured relationship. The second concerns an intervention and its consequences, including changes in the underlying illness and treatment benefit.



Methods

This is a conceptual methods analysis based on reading the named psychosis studies and inspecting the public evidence fields used by UnifiedACB. It is not a systematic review, a registered protocol, or a secondary analysis of participant-level data. The proposed design principles are recommendations for future studies, not methods already applied to a new cohort.

The first step would be to specify the target question in ordinary language and then define its measurable components. These include the population, exposure or intervention contrast, time zero, cognitive outcome, follow-up interval, and competing clinical outcomes. A medication change initiated because cognition has already worsened requires different interpretation from an exposure measured before the outcome.

The second step would be to define the exposure independently of the results. The original source version, identity mapping, route and formulation handling, treatment window, and approach to actual occasional use should be frozen. Source-native categories should remain unchanged. Missing observations should be reported as missing, with the amount of incomplete coverage visible.

The third step would be to distinguish variables according to their role in the question. Baseline illness severity may influence both treatment selection and cognition. A symptom that changes after treatment may instead lie on a pathway through which treatment affects performance. Automatically adjusting for every available variable can therefore change the question being estimated. The intended causal structure should be stated before choosing a model.

The fourth step would be to define the outcome precisely. A cognitive composite, a domain score, functional capacity, and real-world participation should not be combined without justification. Testing conditions, repeated-measure comparability, and the possibility of practice effects need a plan. The analysis should also specify how loss to follow-up and incomplete testing will be described.

Results

No new empirical results are reported. The analysis identifies three distinct possible study outputs: a descriptive association, an estimate for a defined treatment strategy, and a prediction of a future outcome. Each requires different assumptions and evaluation. Success in one does not validate the others.

The published psychosis synthesis by Mancini and colleagues includes burden studies, serological measures, and tapering studies, illustrating why the exposure and design should remain attached to each conclusion. [Mancini et al., 2025](#) The current UnifiedACB source structure can support transparent classification and provenance. It does not itself supply randomization, complete administration histories, or a validated counterfactual model.

Discussion

The main design risk is confounding by indication: the clinical reason for a medicine may also relate to cognition. Another risk is reverse timing, where an emerging outcome changes treatment before



the investigator records exposure. A carefully defined baseline and repeated exposure history can make these problems more visible, but do not guarantee their elimination.

Intervention studies also need to define what is being changed. A review strategy may alter several medicines, improve reconciliation, and increase clinical contact. If cognition improves, the effect belongs initially to that strategy as tested. Attributing the entire effect to a reduction in an ordinal total requires additional evidence. The source category may be a useful process measure without being the sole mechanism.

Reporting should therefore preserve a distinction between the intended intervention, the actual treatment changes, and the outcomes observed. If a study permits individualized decisions, describe that flexibility rather than presenting the intervention as a uniform pharmacologic dose reduction. If some participants cannot change treatment, that is relevant to interpretation and generalizability.

Source sensitivity also deserves attention. A result that appears under one scale and not another may reflect different medication coverage or classification. The appropriate response is to examine those differences and report them. Selecting whichever result is strongest after inspection and presenting it as definitive would conceal an important analytic decision.

Distinguish planned analyses from explanations formed afterward

A future causal study should preserve its initial question and analysis plan, then label changes prompted by unexpected data. An unplanned subgroup pattern may generate a useful hypothesis, but it should not be described as though it was the original confirmatory test. The same applies when an anticipated cognitive association is absent: switching to a different domain or burden definition until a favorable result appears changes the evidential status of the finding.

Exposure errors should also be described in terms of the causal question. A prescription record may be an imperfect measure of medication actually taken, and a single assessment may not represent the period during which an outcome developed. These limitations can remain even when every source classification is extracted correctly. Data fidelity supports the analysis, but it cannot supply the missing temporal or clinical information needed to identify a treatment effect.

Limitations

This article does not supply a complete statistical analysis plan, sample-size calculation, or operational definitions for a particular dataset. Those require the actual population, outcome distribution, follow-up structure, and intended estimand. No claim of registration, ethics approval, recruitment, or independent validation is made.

Even well-designed observational work can retain unmeasured confounding and exposure error. An intervention study may answer a clinically useful strategy question without isolating a single mechanism. Generalization across ages, diagnoses, healthcare settings, or source versions must be evaluated rather than assumed. The framework also does not make ordinal scales interchangeable or justify averaging them.



Conclusion

The research question should determine the design, not emerge from a convenient burden total. Source fidelity is necessary for credible analysis, but causal interpretation additionally requires a clear treatment contrast, chronology, outcome definition, and account of competing explanations. Those requirements remain separate from any success in reproducing a medication lookup.

References

1. Mancini V, et al. Anticholinergic Burden and Cognitive Function in Psychosis: A Systematic Review and Meta-Analysis. *Am J Psychiatry*. 2025;182:349-359. [Source](#)
2. Vennard O, Stewart C, Tolia M, Soiza RL, Myint PK. Anticholinergic Medication Burden Scales: A Systematic Review. *J Am Geriatr Soc*. 2026;74(6):1771-1784. [Source](#)
3. Georgiou R, et al. Anticholinergic Burden and Cognitive Performance in Patients With Schizophrenia: A Systematic Literature Review. *Front Psychiatry*. 2021;12:779607. [Source](#)

Explore the evidence

[Ask UnifiedACB](#) about a medication or source, browse the [Medication Library](#), or read the [methodology](#).

Disclosure

Funding: None. Conflict of interest: None declared for the UnifiedACB educational project.

Educational evidence summary. This content does not provide patient-specific medical advice and does not replace clinical judgment, medication reconciliation, or prescribing guidance.